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NEWS 4	Feb 24	TEMA now available on STN
NEWS 5	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 6	Feb 26	PCTFULL now contains images
NEWS 7	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 8	Mar 24	PATDPAFULL now available on STN
NEWS 9	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 10	Apr 11	Display formats in DGENE enhanced
NEWS 11	Apr 14	MEDLINE Reload
NEWS 12	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 13	Jun 13	Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 14	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 15	Apr 28	RDISCLOSURE now available on STN
NEWS 16	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 17	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 18	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 19	May 19	Simultaneous left and right truncation added to WSCA
NEWS 20	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 21	Jun 06	Simultaneous left and right truncation added to CBNB
NEWS 22	Jun 06	PASCAL enhanced with additional data
NEWS 23	Jun 20	2003 edition of the FSTA Thesaurus is now available
NEWS 24	Jun 25	HSDB has been reloaded

NEWS EXPRESS	April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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FILE COVERS 1907 - 14 Jul 2003 VOL 139 ISS 3
FILE LAST UPDATED: 13 Jul 2003 (20030713/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s us5889061/pn
L1 1 US5889061/PN

=> d l1 abs ibib

L1 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

AB Z(NHZ1NHR)2 [I; R = H or alk(en)yl; Z = BAB; A,Z1 = (cyclo)alk(en)ylene, arylene; B = bond or alk(en)ylene] were prepd. Thus, N,N'-bis(mesitylsulfonyl)-cis-1,2-cyclobutanediamine (prepn. given) was N-alkylated by Br(CH2)3NEtSO2C6H2Me3-2,4,6 to give, after deprotection, Z[NH(CH2)3NHEt]2 (Z = cis-1,2-cyclobutylene). Data for biol. activity of I were given in graphic form.

ACCESSION NUMBER: 1999:212803 CAPLUS

DOCUMENT NUMBER: 130:252086

TITLE: Preparation of conformationally restricted spermine analogs as antineoplastic agents

INVENTOR(S): Frydman, Benjamin J.; Marton, Laurence J.; Reddy, Vendohar K.; Valasinas, Aldonia L.; Witiak, Donald T.

PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA

SOURCE: U.S., 41 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5889061	A	19990330	US 1997-951015	19971015 <--
US 6392098	B1	20020521	US 1999-280278	19990329

PRIORITY APPLN. INFO.: US 1997-951015 A1 19971015

OTHER SOURCE(S): MARPAT 130:252086

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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DICTIONARY FILE UPDATES:  13 JUL 2003  HIGHEST RN 547695-13-6

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  Please note that search-term pricing does apply when
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Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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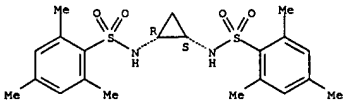
221616-09-7/BI OR 221616-10-0/BI OR 22161

=> d scan

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(1R,2S)-1,2-cyclopropanediylbis[2,4,6-trimethyl-, rel- (9CI)
MF C21 H28 N2 O4 S2

Relative stereochemistry.



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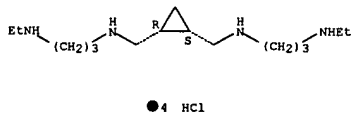
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):68

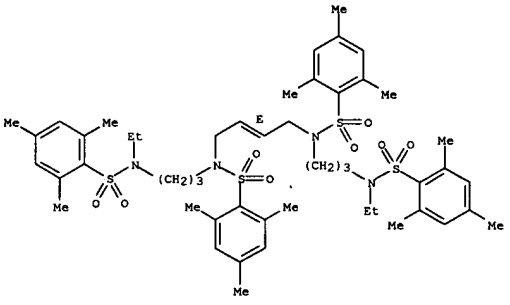
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (1R,2S)-rel- (9CI)
MF C15 H34 N4 . 4 Cl H

Relative stereochemistry.



L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(2E)-2-butene-1,4-diylbis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl- (9CI)
MF C50 H72 N4 O8 S4

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 2-Propenenitrile (9CI)
MF C3 H3 N
CI COM

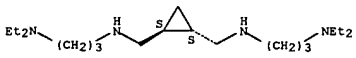
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Propanenitrile, 3-(ethylamino)- (9CI)
MF C5 H10 N2
CI COM

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanamine, N,N'-bis[3-(diethylamino)propyl]-, tetrahydrochloride, (1R,2R)-rel- (9CI)
MF C19 H42 N4 . 4 Cl H

Relative stereochemistry.

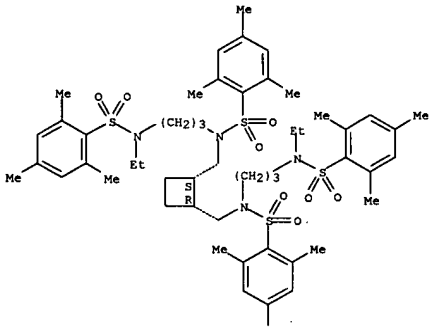


●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-[(1R,2S)-1,2-cyclobutanediylbis(methylene)]bis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl-, rel- (9CI)
MF C52 H76 N4 O8 S4

Relative stereochemistry.

PAGE 1-A



PAGE 2-A

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L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanaminium, N,N,N,N',N',N'-hexamethyl-, dichloride, (1R,2S)-rel- (9CI)
MF C11 H26 N2 . 2 Cl

Relative stereochemistry.

●2 Cl-

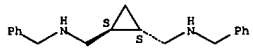
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 2-Butene-1,4-diol, (2Z)- (9CI)
MF C4 H8 O2
CI COM

Double bond geometry as shown.

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanamine, N,N'-bis(phenylmethyl)-, (1R,2R)-rel- (9CI)
MF C19 H24 N2

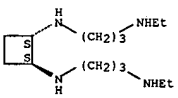
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanediamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (1R,2R)-rel- (9CI)
MF C14 H32 N4 . 4 Cl H

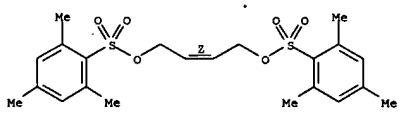
Relative stereochemistry.



●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonic acid, 2,4,6-trimethyl-, (2Z)-2-butene-1,4-diyl ester (9CI)
MF C22 H28 O6 S2

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

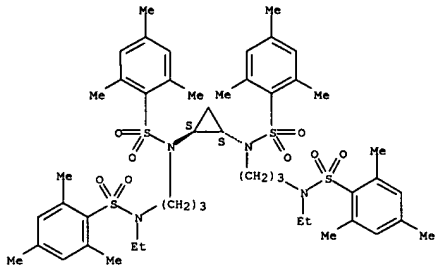
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanol, (1R,2R)-rel- (9CI)
MF C5 H10 O2

Relative stereochemistry.

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(1R,2R)-1,2-cyclopropanediylbis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl-, rel- (9CI)
MF C49 H70 N4 O8 S4

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanediamine, dihydrochloride, (1R,2R)-rel- (9CI)
MF C4 H10 N2 . 2 Cl H

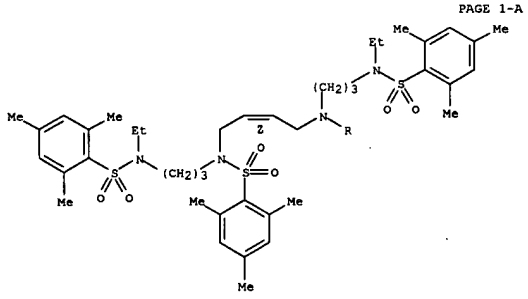
Relative stereochemistry.

●2 HCl

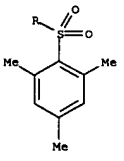
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(2Z)-2-butene-1,4-diylbis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl- (9CI)
MF C50 H72 N4 O8 S4

Double bond geometry as shown.

PAGE 1-A



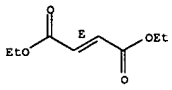
PAGE 2-A



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 2-Butenedioic acid (2E)-, diethyl ester (9CI)
MF C8 H12 O4
CI COM

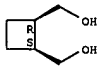
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanedimethanol, (1R,2S)-rel- (9CI)
MF C6 H12 O2

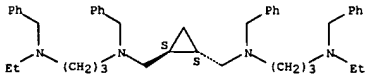
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanamine, N,N'-bis[3-[ethyl(phenylmethyl)amino]propyl]-N,N'-bis(phenylmethyl)-, (1R,2R)-rel- (9CI)
MF C43 H58 N4

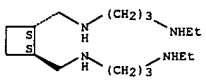
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanedimethanamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (1R,2R)-rel- (9CI)
MF C16 H36 N4 . 4 Cl H

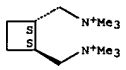
Relative stereochemistry.



●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanedimethanaminium, N,N,N,N',N',N'-hexamethyl-, dichloride, (1R,2R)-rel- (9CI)
MF C12 H28 N2 . 2 Cl

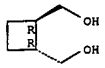
Relative stereochemistry.



●2 Cl⁻

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanedimethanol, (1R,2R)-rel- (9CI)
MF C6 H12 O2

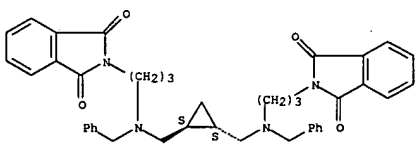
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-Isoindole-1,3(2H)-dione, 2,2'-[(1R,2R)-1,2-cyclopropanediylbis[methylene[(phenylmethyl)imino]-3,1-propanediyl]]bis-, rel- (9CI)
MF C41 H42 N4 O4

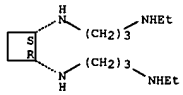
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

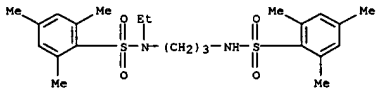
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanediamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (1R,2S)-rel- (9CI)
MF C14 H32 N4 . 4 Cl H

Relative stereochemistry.



●4 HCl

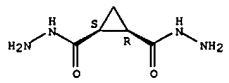
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N-ethyl-2,4,6-trimethyl-N-[3-[[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]- (9CI)
MF C23 H34 N2 O4 S2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedicarboxylic acid, dihydrazide, (1R,2S)-rel- (9CI)
MF C5 H10 N4 O2

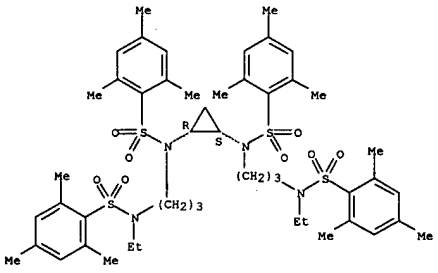
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(1R,2S)-1,2-cyclopropanediylbis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl-, rel- (9CI)
MF C49 H70 N4 O8 S4

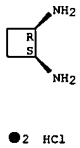
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

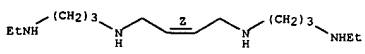
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanediamine, dihydrochloride, (1R,2S)-rel- (9CI)
MF C4 H10 N2 . 2 Cl H

Relative stereochemistry.



L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS .
IN 2-Butene-1,4-diamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (2Z)- (9CI)
MF C14 H32 N4 . 4 Cl H

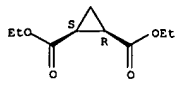
Double bond geometry as shown.



●4 HCl

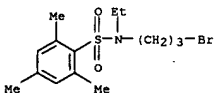
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedicarboxylic acid, diethyl ester, (1R,2S)-rel- (9CI)
MF C9 H14 O4

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

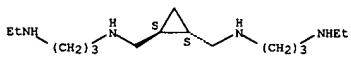
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N-(3-bromopropyl)-N-ethyl-2,4,6-trimethyl- (9CI)
MF C14 H22 Br N O2 S



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (1R,2R)-rel- (9CI)
MF C15 H34 N4 . 4 Cl H

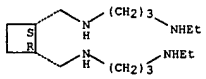
Relative stereochemistry.



●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanedimethanamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (1R,2S)-rel- (9CI)
MF C16 H36 N4 . 4 Cl H

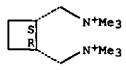
Relative stereochemistry.



●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanedimethanaminium, N,N,N,N',N',N'-hexamethyl-, dichloride, (1R,2S)-rel- (9CI)
MF C12 H28 N2 . 2 Cl

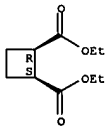
Relative stereochemistry.



●2 Cl^-

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanedicarboxylic acid, diethyl ester, (1R,2S)-rel- (9CI)
MF C10 H16 O4

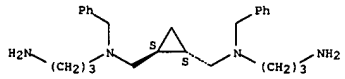
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanamine, N,N'-bis(3-aminopropyl)-N,N'-bis(phenylmethyl)-, (1R,2R)-rel- (9CI)
MF C25 H38 N4

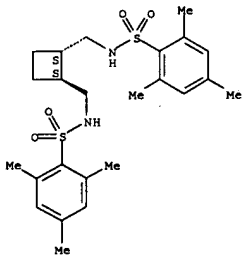
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-[(1R,2R)-1,2-cyclobutanediylbis(methylene)]bis[2,4,6-trimethyl-, rel- (9CI)
MF C24 H34 N2 O4 S2

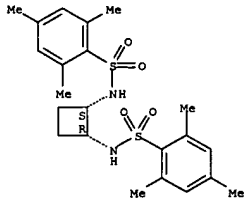
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(1R,2S)-1,2-cyclobutanediylbis[2,4,6-trimethyl-, rel- (9CI)
MF C22 H30 N2 O4 S2

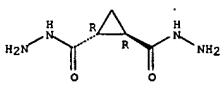
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedicarboxylic acid, dihydrazide, (1R,2R)-rel- (9CI)
MF C5 H10 N4 O2
CI COM

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

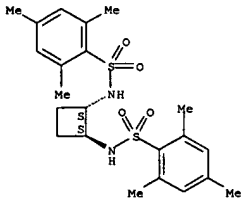
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanediamine; N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (1R,2R)-rel- (9CI)
MF C13 H30 N4 . 4 Cl H

Relative stereochemistry.

●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(1R,2R)-1,2-cyclobutanediylbis[2,4,6-trimethyl-, rel- (9CI)
MF C22 H30 N2 O4 S2

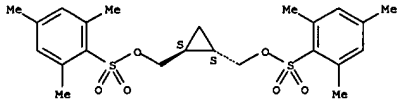
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

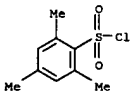
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonic acid, 2,4,6-trimethyl-, (1R,2R)-1,2-cyclopropanediylbis(methylene) ester, rel- (9CI)
MF C23 H30 O6 S2

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

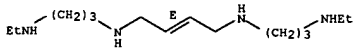
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonyl chloride, 2,4,6-trimethyl- (9CI)
MF C9 H11 Cl O2 S



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 2-Butene-1,4-diamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (2E)- (9CI)
MF C14 H32 N4 . 4 Cl H

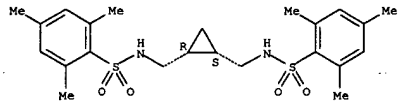
Double bond geometry as shown.



●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-[(1R,2S)-1,2-cyclopropanediylbis(methylene)]bis[2,4,6-trimethyl-, rel- (9CI)
MF C23 H32 N2 O4 S2

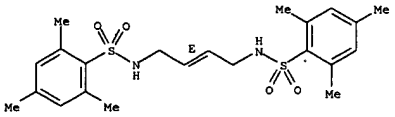
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(2E)-2-butene-1,4-diylbis[2,4,6-trimethyl- (9CI)
MF C22 H30 N2 O4 S2

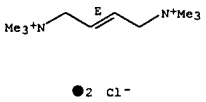
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 2-Butene-1,4-diaminium, N,N,N,N',N',N'-hexamethyl-, dichloride, (2E)- (9CI)
MF C10 H24 N2 . 2 Cl

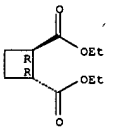
Double bond geometry as shown.



●2 Cl⁻

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclobutanedicarboxylic acid, diethyl ester, (1R,2R)-rel- (9CI)
MF C10 H16 O4

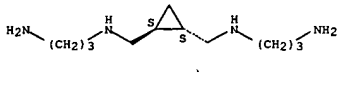
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanamine, N,N'-bis(3-aminopropyl)-, tetrahydrochloride, (1R,2R)-rel- (9CI)
MF C11 H26 N4 . 4 Cl H

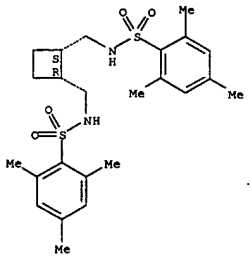
Relative stereochemistry.



●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-[(1R,2S)-1,2-cyclobutanediylbis(methylene)]bis[2,4,6-trimethyl-, rel- (9CI)
MF C24 H34 N2 O4 S2

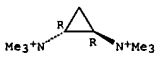
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanediaminium, N,N,N,N',N',N'-hexamethyl-, dichloride, (1R,2R)-rel- (9CI)
MF C9 H22 N2 . 2 Cl

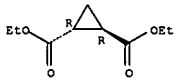
Relative stereochemistry.



●2 Cl-

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedicarboxylic acid, diethyl ester, (1R,2R)-rel- (9CI)
MF C9 H14 O4

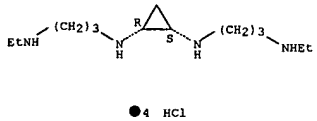
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanediamine, N,N'-bis[3-(ethylamino)propyl]-, tetrahydrochloride, (1R,2S)-rel- (9CI)
MF C13 H30 N4 . 4 Cl H

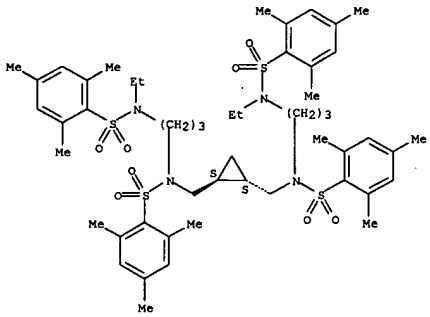
Relative stereochemistry.



●4 HCl

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-[1,2-cyclopropanediylbis(methylene)]bis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl-, (1R,2R)-rel- (9CI)
MF C51 H74 N4 O8 S4

Relative stereochemistry.

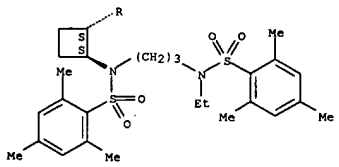


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

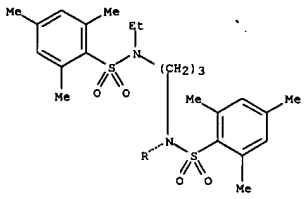
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(1R,2R)-1,2-cyclobutanediylbis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl-, rel- (9CI)
MF C50 H72 N4 O8 S4

Relative stereochemistry.

PAGE 1-A



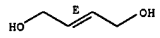
PAGE 2-A



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 2-Butene-1,4-diol, (2E)- (9CI)
MF C4 H8 O2
CI COM

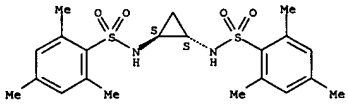
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide,
N,N'-(1R,2R)-1,2-cyclopropanediylbis[2,4,6-trimethyl-,
rel- (9CI)
MF C21 H28 N2 O4 S2

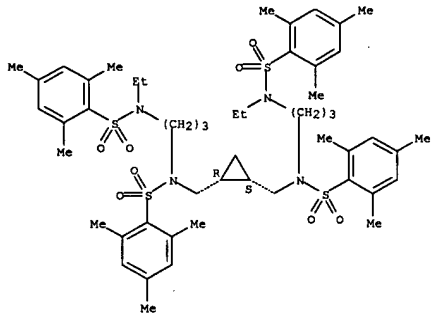
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide,
N,N'-[(1R,2S)-1,2-cyclopropanediylbis(methylene)]bis[N-
[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl-,
rel- (9CI)
MF C51 H74 N4 O8 S4

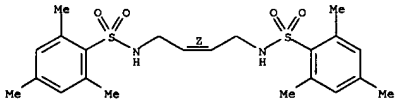
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(2Z)-2-butene-1,4-diylbis[2,4,6-trimethyl- (9CI)
MF C22 H30 N2 O4 S2

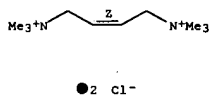
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 2-Butene-1,4-diaminium, N,N,N,N',N',N'-hexamethyl-, dichloride, (2Z)-
(9CI)
MF C10 H24 N2 . 2 Cl

Double bond geometry as shown.



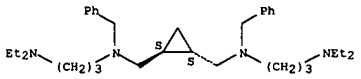
●2 Cl⁻

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,3-Propanediamine, N-ethyl- (7CI, 8CI, 9CI)
MF C5 H14 N2
CI COM

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanamine, N,N'-bis[3-(diethylamino)propyl]-N,N'-bis(phenylmethyl)-, (1R,2R)-rel- (9CI)
MF C33 H54 N4

Relative stereochemistry.

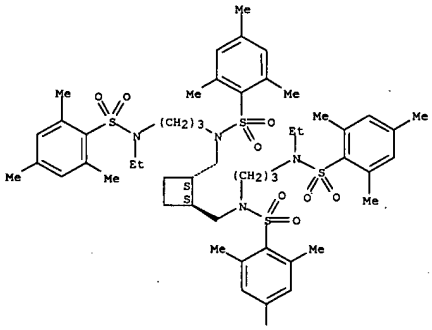


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-[(1R,2R)-1,2-cyclobutanediylbis(methylene)]bis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl-, rel- (9CI)
MF C52 H76 N4 O8 S4

Relative stereochemistry.

PAGE 1-A

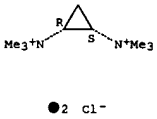


PAGE 2-A

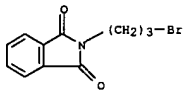
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanediaminium, N,N,N,N',N',N'-hexamethyl-, dichloride, (1R,2S)-rel- (9CI)
MF C9 H22 N2 . 2 Cl

Relative stereochemistry.



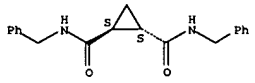
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1H-Isoindole-1,3(2H)-dione, 2-(3-bromopropyl)- (9CI)
MF C11 H10 Br N O2
CI COM



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedicarboxamide, N,N'-bis(phenylmethyl)-, (1R,2R)-rel- (9CI)
MF C19 H20 N2 O2

Relative stereochemistry.

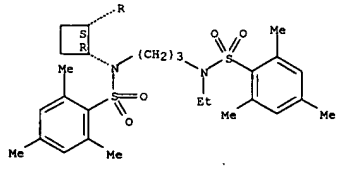


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

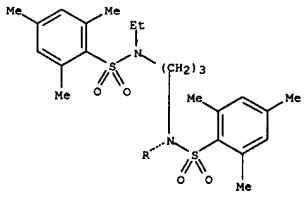
L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonamide, N,N'-(1R,2S)-1,2-cyclobutanediylbis[N-[3-[ethyl[(2,4,6-trimethylphenyl)sulfonyl]amino]propyl]-2,4,6-trimethyl-, rel- (9CI)
MF C50 H72 N4 O8 S4

Relative stereochemistry.

PAGE 1-A



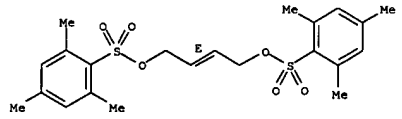
PAGE 2-A



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Benzenesulfonic acid, 2,4,6-trimethyl-, (2E)-2-butene-1,4-diyl ester (9CI)
MF C22 H28 O6 S2

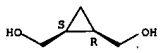
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 69 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN 1,2-Cyclopropanedimethanol, (1R,2S)-rel- (9CI)
MF C5 H10 O2

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

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=>  fil reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         4.00       8.85

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -0.65

FILE 'REGISTRY' ENTERED AT 17:32:26 ON 14 JUL 2003
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STRUCTURE FILE UPDATES:   13 JUL 2003  HIGHEST RN 547695-13-6
DICTIONARY FILE UPDATES:  13 JUL 2003  HIGHEST RN 547695-13-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09560711.str

L3      STRUCTURE UPLOADED

=> d query
L3              STR
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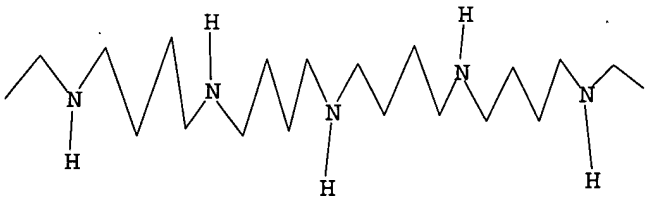


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Structure attributes must be viewed using STN Express query preparation.


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SAMPLE SEARCH INITIATED 17:32:41 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -  22323 TO ITERATE

  4.5% PROCESSED    1000 ITERATIONS                              0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01
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FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       437534 TO   455386
PROJECTED ANSWERS:               0 TO        0

L4            0 SEA SSS SAM L3

=> s l3 full
FULL SEARCH INITIATED 17:32:44 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 445356 TO ITERATE

 89.8% PROCESSED  400000 ITERATIONS                          147 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.10

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       445356 TO   445356
PROJECTED ANSWERS:             147 TO      201

L5          147 SEA SSS FUL L3

=> fil caplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                  ENTRY    SESSION
FULL ESTIMATED COST                               148.15     157.00

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                  ENTRY    SESSION
CA SUBSCRIBER PRICE                                 0.00      -0.65

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FILE COVERS 1907 - 14 Jul 2003  VOL 139 ISS 3
FILE LAST UPDATED: 13 Jul 2003  (20030713/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s l5
L6          120 L5

=> d l6 100-120 abs ibib hitstr
```

L6 ANSWER 100 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB Polyglutamyl derivs. of methotrexate (MTX) and 10-deazaaminopterin (10-DAM) contg. 1-6 glutamate residues (Glu residues) were tested as inhibitors of dihydrofolate reductase (DHFR) derived from sheep, chicken, and beef liver. The ability of dihydropteroylpentaglutamate to antagonize the inhibitory activity of the analogs was also studied. The most striking effects were seen with sheep liver DHFR, where polyglutamylation of MTX causes stepwise decreases in the concn. required for 50% inhibition (IC50) with each addnl. Glu residue until MTX with a total of 6 Glu residues has an IC50 value 1/3 that of MTX. With 10-DAM the pattern is more complex. The IC50 values increase with 10-DAM having a total of 3 Glu residues which has a value twice that of 10-DAM. 10-DAM with a total of 4 Glu residues and 10-DAM with a total of 5 Glu residues have progressively lower IC50 values, the latter being equipotent with 10-DAM. With dihydropteroylpentaglutamate as substrate instead of dihydrofolate, the IC50 values are increased 2-5-fold for MTX and 10-DAM derivs. The results obtained with chicken and beef liver DHFR are generally similar to those described for the sheep liver enzyme, but the effects of polyglutamylation are less pronounced. The addn. of 0.2M KCl to the assay system reduces the differences in inhibitory potency of the polyglutamyl derivs. with all 3 enzymes tested. Thus, polyglutamylation can alter the interaction of folate analogs and dihydrofolate with DHFR.

ACCESSION NUMBER: 1989:526465 CAPLUS
Correction of: 1987:470236
DOCUMENT NUMBER: 111:126465
Correction of: 107:70236
TITLE: Interaction of polyglutamyl derivatives of methotrexate, 10-deazaaminopterin, and dihydrofolate with dihydrofolate reductase
AUTHOR(S): Kumar, Piyush; Kisliuk, Roy L.; Gaumont, Yvette; Nair, Madhavan G.; Baugh, Charles M.; Kaufman, Bernard T.
CORPORATE SOURCE: Dep. Biochem. Pharmacol., Tufts Univ. Health Sci. Campus, Boston, MA, 02111, USA
SOURCE: Cancer Research (1986), 46(10), 5020-3
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **105099-96-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of and dihydrofolate reductase inhibition by)

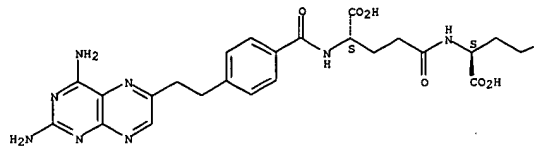
RN 105099-96-5 CAPLUS

CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

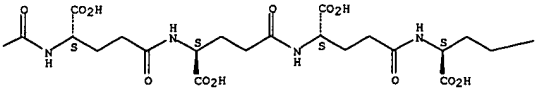
Absolute stereochemistry.

L6 ANSWER 100 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



PAGE 1-B



PAGE 1-C

L6 ANSWER 101 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB Coenzyme F420 was assayed by HPLC with fluorimetric detection; this permits quantification of individual coenzyme F420 analogs while avoiding the inclusion of interfering material. The total intracellular coenzyme F420 content of M. barkeri MS cultivated on MeOH and on H2-CO2 and of M. mazei S-6 cultured on MeOH remained relatively const. during batch growth. The most abundant analogs in M. barkeri were coenzymes F420-2 and F420-4, while in M. mazei coenzymes F420-2 and F420-3 predominated. Significant changes in the relative proportions of the coenzyme F420 analogs were noted during batch growth, with coenzymes F420-2 and F420-4 showing opposite responses to each other and the same being also true for coenzymes F420-3 and F420-5. This suggests that an enzyme responsible for transferring pairs of glutamic acid residues may be active. The degrdn. fragment FO was also detected in cells in late exponential and stationary phase. Coenzyme F420 analogs were present in the culture supernatant of both methanogens, in similar proportions to that in the cells, except for FO which was principally located in the supernatant.

ACCESSION NUMBER: 1989:228244 CAPLUS
DOCUMENT NUMBER: 110:228244
TITLE: Changes in concentrations of coenzyme F420 analogs during batch growth of Methanosarcina barkeri and Methanosarcina mazei
AUTHOR(S): Peck, Michael W.
CORPORATE SOURCE: Inst. Food Res., Agric. Food Res. Counc., Norwich, NR4 7UA, UK
SOURCE: Applied and Environmental Microbiology (1989), 55(4), 940-5
CODEN: AEMIDF; ISSN: 0099-2240
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **108260-38-4**
RL: BIOL (Biological study)
(of Methanosarcina barkeri and M. mazei)

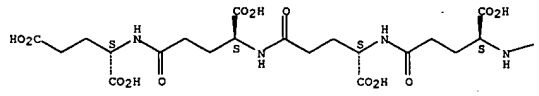
RN 108260-38-4 CAPLUS

CN L-Glutamic acid, N-{(2S)-1-oxo-2-(phosphonooxy)propyl]-L-.gamma.-glutamyl-L-.gamma.-glutamyl-L-.gamma.-glutamyl-L-.gamma.-glutamyl-, P.fwdarw.5-ester with 1-deoxy-1-(3,4-dihydro-8-hydroxy-2,4-dioxopyrimido[4,5-b]quinolin-10(2H)-yl)-D-ribitol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 101 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



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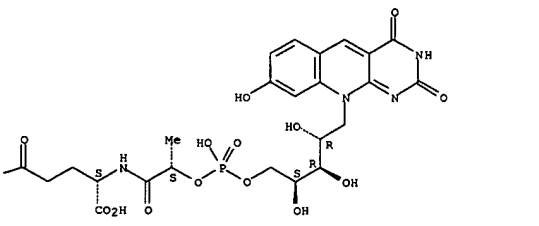


L6 ANSWER 102 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB Polyglutamylation of methotrexate, 10-deazaaminopterin, 10-ethyl-10-deazaaminopterin, and aminopterin increased their potency in inhibiting human dihydrofolate reductase when the substrate was monoglutamylated folic acid. Polyglutamylation of the substrate folic acid reduced the potency of all drugs, except 10-deazaaminopterin. However, the polyglutamates of all drugs still were more potent than the parent drugs.

ACCESSION NUMBER: 1989:205060 CAPLUS
DOCUMENT NUMBER: 110:205060
TITLE: Inhibition of human dihydrofolate reductase by antifolyl polyglutamates
AUTHOR(S): Kumar, Piyush; Kisliuk, Roy L.; Gaumont, Yvette; Freisheim, James H.; Nair, Madhavan G.
CORPORATE SOURCE: Dep. Biochem., Tufts Univ., Boston, MA, 02111, USA
SOURCE: Biochemical Pharmacology (1989), 38(3), 541-3
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

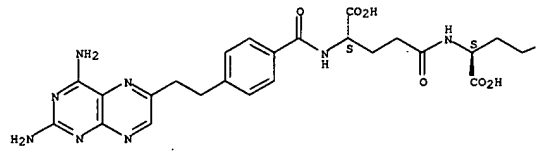
IT **105099-96-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of and dihydrofolate reductase inhibition by, structure in relation to, in humans)

RN 105099-96-5 CAPLUS

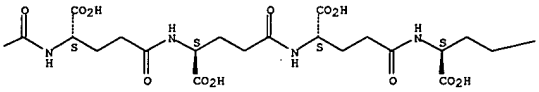
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L6 ANSWER 102 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-C

L6 ANSWER 103 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB In order to det. the biochem. basis for the cytotoxicity of homofolates, poly-.gamma.-glutamyl derivs. of homofolate (HPteGlu) and tetrahydrohomofolate (H4HPteGlu) were tested as inhibitors of glycinamide ribonucleotide formyltransferase (GARFT), aminoimidazolecarboxamide ribonucleotide formyltransferase (AICARFT), thymidylate synthase, and serine hydroxymethyltransferase (SHMT) in exts. of Manca human lymphoma and L1210 murine leukemia cells. The most striking inhibitions are that of GARFT by (6R,S)-H4HPte Glu4-6 with IC50 values from 1.3 to 0.3 .mu.M. Both diastereomers, (6R)-H4HPteGlu6 and (6S)-H4HPteGlu6, inhibit GARFT activity. In Manca cell exts., the (6S)-form is more potent than the (6R)-form, whereas in the murine system the reverse is true. The (6R,S)-H4HPteGlu polyglutamates are weak inhibitors of human AICARFT (IC50, 6-10 .mu.M). Polyglutamates of HPteGlu, however, are more inhibitory to AICARFT, with HPteGlu4-6 having IC50 values close to 2 .mu.M. Polyglutamates of HPteGlu and of H4HPteGlu are weaker inhibitors of thymidylate synthase (IC50, 8 .mu.M for HPteGlu5-6 and >20 .mu.M for H4HPteGlu1-5). Polyglutamates of HPteGlu and of H4HPteGlu are poor inhibitors of SHMT (IC50, >20 .mu.M). Manca cell growth is inhibited 50% by HPteGlu and (6R,S)-5-methyl-H4HPteGlu at 6 and 8 .mu.M, resp. Both of these effects are reversed by 0.1 mM inosine. Trimetrexate at a subinhibitory concn., 10 nM, antagonizes growth inhibition by HPteGlu, raising the IC50 from 6 to 64 .mu.M, but enhances inhibition by (6R,S)-5-methyl-H4HPteGlu, lowering the IC50 from 8 to 5 .mu.M. These results support the view that homofolates become toxic after conversion to H4HPteGlu polyglutamates which block GARFT, a step in purine biosynthesis.

ACCESSION NUMBER: 1989:147307 CAPLUS
DOCUMENT NUMBER: 110:147307
TITLE: Inhibition of glycinamide ribonucleotide formyltransferase and other folate enzymes by homofolate polyglutamates in human lymphoma and murine leukemia cell extracts
AUTHOR(S): Thorndike, J.; Gaumont, Y.; Kisliuk, R. L.; Sirotnak, F. M.; Murthy, B. R.; Nair, M. G.; Piper, J. R.
CORPORATE SOURCE: Dep. Biochem., Tufts Univ., Boston, MA, 02111, USA
SOURCE: Cancer Research (1989), 49(1), 158-63
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **119740-44-2 119740-48-6 119764-51-1 119817-16-2**
RL: BIOL (Biological study)
(folate enzymes inhibition by, in human lymphoma and murine leukemia cell exts.)

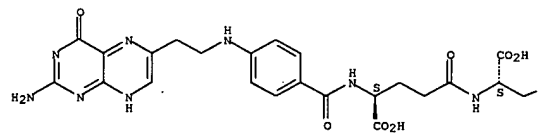
RN 119740-44-2 CAPLUS

CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[[2-(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)ethyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

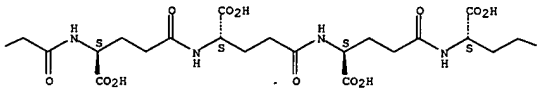
Absolute stereochemistry.

L6 ANSWER 103 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



PAGE 1-B



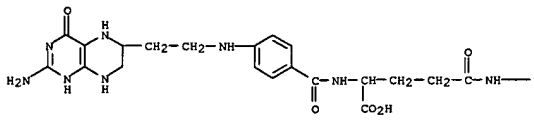
PAGE 1-C

RN 119740-48-6 CAPLUS

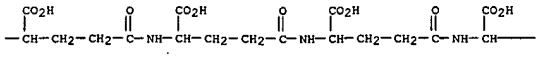
CN L-Glutamic acid, N-[N-[N-[N-[N-[N-[4-[[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)ethyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, (S)- (9CI) (CA INDEX NAME)

L6 ANSWER 103 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

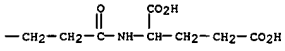
PAGE 1-A



PAGE 1-B



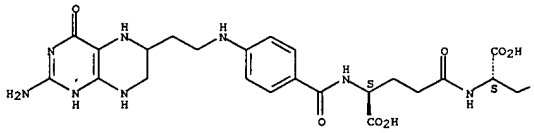
PAGE 1-C



RN 119764-51-1 CAPLUS
CN L-Glutamic acid,
N-[N-[N-[N-[N-[N-[4-[[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)ethyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-(9CI) (CA INDEX NAME)

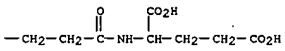
Absolute stereochemistry.

PAGE 1-A



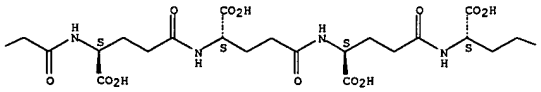
L6 ANSWER 103 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-C



L6 ANSWER 103 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

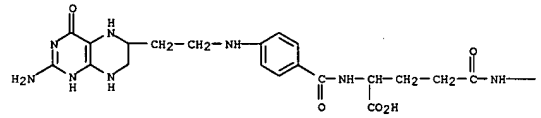
PAGE 1-B



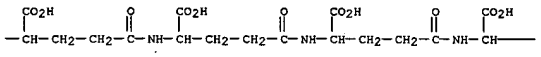
PAGE 1-C

RN 119817-16-2 CAPLUS
CN L-Glutamic acid,
N-[N-[N-[N-[N-[N-[4-[[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)ethyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, (R)- (9CI) (CA INDEX NAME)

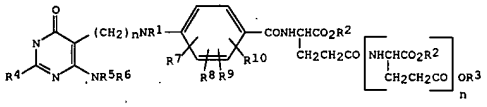
PAGE 1-A



PAGE 1-B



L6 ANSWER 104 OF 120 CAPLUS COPYRIGHT 2003 ACS
GI



I

AB The title compds. (I; R1 = H, C1-4 alkyl, Ac, CHO; R2, R3 = H, C1-4 alkyl; R4 = NR11R12; R5, R6, R11, R12 = H, C1-4 alkyl, C1-12 acyl; R7, R8, R9, R10 = H, halo, C1-4 haloalkyl, C1-4 alkyl, alkoxy; n = 2-5; m = 0-6) and salts thereof were prepd. as neoplasm inhibitors. 3-(2-Acetylamino-4-diacetylamino-1,6-dihydro-6-oxo-5-pyrimidinyl)propionaldehyde (prepn. given) and di-Me N-(4-aminobenzoyl)-L-glutamate were stirred with 3.ANG. mol. sieves in HOAc for 1 h followed by addn. of NaBH3CN to give

N-[4-[3-(2,4-diamino-1,6-dihydro-6-oxo-5-pyrimidinyl)propylamino]benzoyl]-L-glutamic acid (II). II increased the lifespan of mice with P388 tumors by 80% at 10 mg/kg i.p. every 4 h.

ACCESSION NUMBER: 1989:39366 CAPLUS
DOCUMENT NUMBER: 110:39366
TITLE: Preparation and testing of oxopyrimidinylbenzoylglutamates as neoplasm inhibitors
and agrochemical microbiocides
INVENTOR(S): Kelley, James Leroy
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

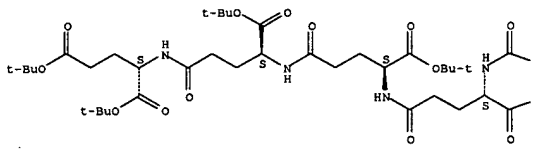
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 268377	A2	19880525	EP 1987-309165	19871016
EP 268377	A3	19881228		
EP 268377	B1	19920318		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AU 8779871	A1	19880421	AU 1987-79871	19871016
AU 598307	B2	19900621		
JP 63126868	A2	19880530	JP 1987-261498	19871016
ZA 8707801	A	19890530	ZA 1987-7801	19871016
US 4880812	A	19891114	US 1987-109225	19871016
AT 73780	E	19920415	AT 1987-309165	19871016
CA 1300807	A1	19920512	CA 1987-549535	19871016
ES 2030735	T3	19921116	ES 1987-309165	19871016

PRIORITY APPLN. INFO.: GB 1986-25019 19861018
EP 1987-309165 19871016
OTHER SOURCE(S): MARPAT 110:39366
IT **118252-57-6P 118252-58-7P 118252-59-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)

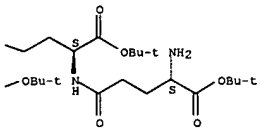
L6 ANSWER 104 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)
(prepn. of, as intermediate for neoplasm inhibitor)
RN 118252-57-6 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-(N-L-.gamma.-glutamyl-L-.gamma.-glutamyl)-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, heptakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

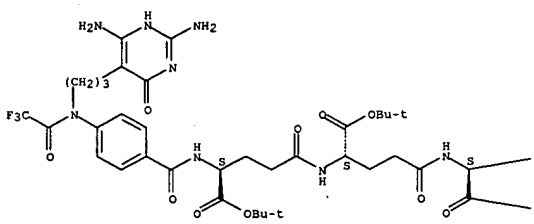


RN 118252-58-7 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)propyl](trifluoroacetyl)amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, heptakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

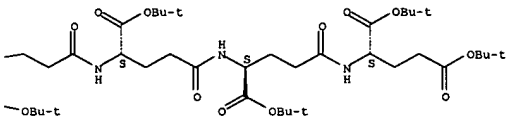
Absolute stereochemistry.

L6 ANSWER 104 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



PAGE 1-B

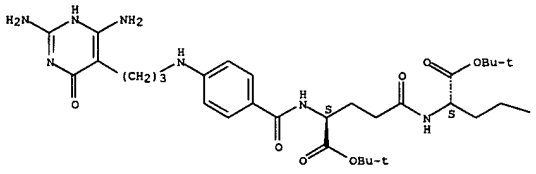


RN 118252-59-8 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)propyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, heptakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

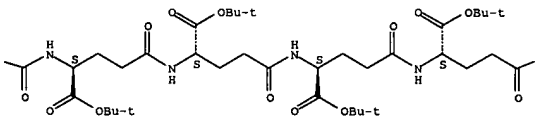
Absolute stereochemistry.

L6 ANSWER 104 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



PAGE 1-B

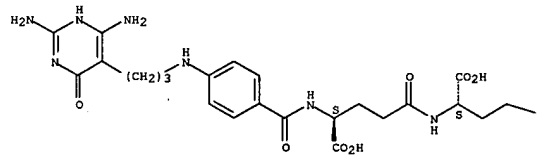


PAGE 1-C

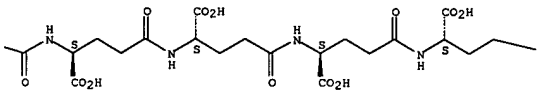
IT 118252-60-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as neoplasm inhibitor)
RN 118252-60-1 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)propyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

L6 ANSWER 104 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 1-C

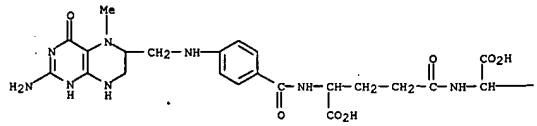
L6 ANSWER 105 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB Thymidylate synthase was purified >4000-fold from a human colon adenocarcinoma maintained as a xenograft in immune-deprived mice. In this disease, the enzyme is an important target for the cytotoxic action of 5-fluorouracil, which is influenced by the reduced folate substrate, 5,10-methylenentetrahydrofolate (CH2-H4PteGlu). Due to the importance of this interaction, and the existence in cells of folate species as polyglutamyl forms, the interaction of folylpolyglutamates with thymidylate synthase was examd. Polyglutamates of folic acid (PteGlu) were used as inhibitors, and the interaction of CH2-H4PteGlu polyglutamates as substrates or in an inhibitory ternary complex were also examd. Using PteGlu1-7, Ki values were detd. A maximal 125-fold decreased in Ki was obsd. between PteGlu1 and PteGlu4; further addn. of up to 3 glutamyl residues did not result in an addnl. decrease in Ki. Despite the increased binding affinity of folylpolyglutamates for this enzyme, no change in the Km values for either dUMP (3.6 .mu.M) of CH2-H4PteGlu (4.3 .mu.M) were detected when polyglutamates of (6R)-CH2-H4PteGlu were used as substrates. Prodn. inhibition studies demonstrated competitive inhibition between dTMP and dUMP in the presence of CH2-H4PteGlu5. In addn., CH2-H4PteGlu4 stabilized an inhibitory ternary complex formed between 5-fluoro-dUMP, thymidylate synthase, and CH2-H4PteGlu4. Thus, the data do not support a change in the order of substrate binding and product release upon polyglutamylation of CH2-H4PteGlu reported for nonhuman mammalian enzyme. This is the 1st study to characterize kinetically thymidylate synthase from a human colon adenocarcinoma.

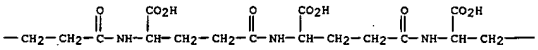
ACCESSION NUMBER: 1988:218049 CAPLUS
DOCUMENT NUMBER: 108:218049
TITLE: Characteristics of thymidylate synthase purified from a human colon adenocarcinoma
AUTHOR(S): Radparvar, Saeed; Houghton, Peter J.; Houghton, Janet A.
CORPORATE SOURCE: Div. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, 38101, USA
SOURCE: Archives of Biochemistry and Biophysics (1988), 260(1), 342-50
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **113776-25-3 113829-43-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thymidylate synthase of human colon adenocarcinoma, kinetics of)
RN 113776-25-3 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, (R)- (9CI) (CA INDEX NAME)

L6 ANSWER 105 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

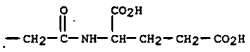
PAGE 1-A



PAGE 1-B

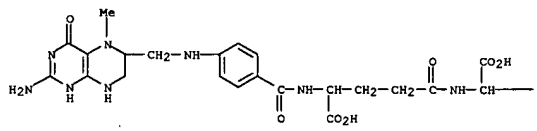


PAGE 1-C



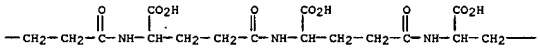
RN 113829-43-9 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, (R)- (9CI) (CA INDEX NAME)

PAGE 1-A

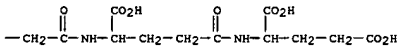


L6 ANSWER 105 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B



PAGE 1-C



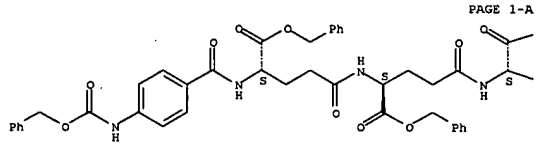
L6 ANSWER 106 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB N-(4-Aminobenzoyl)-.gamma.-oligo(L-glutamic acid)s contg. from two to six glutamic residues have been prepd. in soln. using N.alpha.-Boc-.alpha.-Bzl protections and iso-Bu chlorocarbonate activation. Key steps in the synthesis were the coupling of .gamma.-oligo(.alpha.-benzyl L-glutamate) benzyl esters with N-(4-benzyloxycarbonylaminobenzoyl)-L-glutamic acid .alpha.-benzyl ester and subsequent catalytic hydrogenolysis.

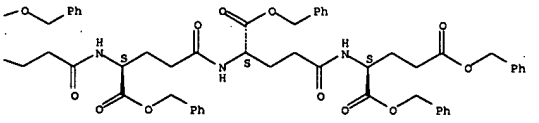
ACCESSION NUMBER: 1988:187256 CAPLUS
DOCUMENT NUMBER: 108:187256
TITLE: Synthesis of N-(4-aminobenzoyl)-.gamma.-oligo(L-glutamic acid)s
AUTHOR(S): Krzyzanowski, Leszek; Rzeszotarska, Barbara
CORPORATE SOURCE: Inst. Chem., Pedagog. Univ., Opole, Pol.
SOURCE: International Journal of Peptide & Protein Research (1987), 29(6), 672-7
CODEN: IJPPC3; ISSN: 0367-8377
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 108:187256
IT **114177-37-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and deblocking of)
RN 114177-37-6 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[[(phenylmethoxy)carbonyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, heptakis(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L6 ANSWER 107 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB An improved method for sepg. analogs of coenzyme F420 by isocratic reversed-phase HPLC is described. The method offers improved resoln., shorter chromatog. runs (.ltoreq.30 min) and requires less complex app. This method can be used to identify the bacterial species from which the coenzyme F420 analogs are obtained.

ACCESSION NUMBER: 1988:108545 CAPLUS
DOCUMENT NUMBER: 108:108545
TITLE: Improved assay of coenzyme F420 analogs from methanogenic bacteria
AUTHOR(S): Peck, Michael W.; Archer, David B.
CORPORATE SOURCE: Inst. Food Res., AFRC, Norwich, NR4 7UA, UK
SOURCE: Biotechnology Techniques (1987), 1(4), 279-84
CODEN: BTECE6; ISSN: 0951-208X
DOCUMENT TYPE: Journal
LANGUAGE: English

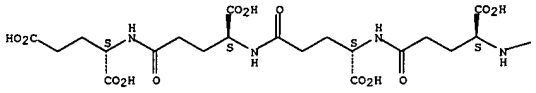
IT **108260-38-4**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, of methanogenic bacteria, by HPLC)

RN 108260-38-4 CAPLUS

CN L-Glutamic acid, N-[(2S)-1-oxo-2-(phosphonooxy)propyl]-L-.gamma.-glutamyl-L-.gamma.-glutamyl-L-.gamma.-glutamyl-L-.gamma.-glutamyl-, P.fwdarw.5-ester with 1-deoxy-1-(3,4-dihydro-8-hydroxy-2,4-dioxopyrimido[4,5-b]quinolin-10(2H)-yl)-D-ribitol (9CI) (CA INDEX NAME)

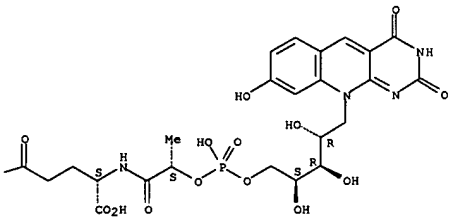
Absolute stereochemistry.

PAGE 1-A



L6 ANSWER 107 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B



L6 ANSWER 108 OF 120 CAPLUS COPYRIGHT 2003 ACS

GI For diagram(s), see printed CA Issue.

AB Poly-.gamma.-glutamate analogs of 10-deazaaminopterin (10-DAAM) I (R = H, n = 0-4) and 10-ethyl-10-deazaaminopterin (10-EDAAM) I (R = Et, n = 0-3) were prepd. by solid-phase procedures. Pteroic acid analogs II (R = H, Et) were coupled with resin-bound poly(.alpha.-benzyl .gamma.-glutamates) by the mixed anhydride method and the resulting resin-bound products were cleaved by 2N NaOH/dioxane to give I. The synthetic products were identical with the poly-.gamma.-glutamyl metabolites of radiolabeled 10-DAAM and 10-EDAAM produced by normal mouse tissues with regard to elution vol. from [(diethylamino)ethyl]cellulose columns and susceptibility to hydrolysis by human plasma folylpolyglutamate hydrolase. Poly-.gamma.-glutamyl metabolites with a glutamate chain length .ltoreq.4 were detected in the tissues. The antifolate activity was evaluated with methotrexate (MTX)-sensitive and MTX-resistant strains of Lactobacilus casei and Streptococcus faecium. In general, inhibitory potency decreases with increasing Glu chain length, however there are two exceptions. Addn. of one Glu residue to 10-DAAM enhances its potency for MTX-resistant L. casei and addn. of one Glu residue to 10-EDAAM enhances its potency for the MTX-sensitive L. casei. Polyglutamylation greatly enhances the inhibitory potency of 10-DAAM and 10-EDAAM for L. casei thymidylate synthase. MTX polyglutamates are 15-30 times more inhibitory than the corresponding 10-DAAM derivs. and 30-60 times more inhibitory than the corresponding 10-EDAAM derivs. Polyglutamylation of 10-DAAM had little influence on its ability to inhibit L. casei dihydrofolate reductase; however, with 10-EDAAM, addn. one or two Glu residues enhanced its inhibitory potency 2.3-fold.

ACCESSION NUMBER: 1988:75842 CAPLUS
DOCUMENT NUMBER: 108:75842
TITLE: Synthesis and biological evaluation of poly-.gamma.-glutamyl metabolites of 10-deazaaminopterin and 10-ethyl-10-deazaaminopterin
AUTHOR(S): Nair, M. G.; Nanavati, N. T.; Kumar, P.; Gaumont, Y.; Kisliuk, R. L.
CORPORATE SOURCE: Dep. Biochem., Univ. South Alabama, Mobile, AL, 36688, USA
SOURCE: Journal of Medicinal Chemistry (1988), 31(1), 181-5
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **112400-12-1D**, resin-bound
RL: RCT (Reactant); RACT (Reactant or reagent)
(partial deblocking of)

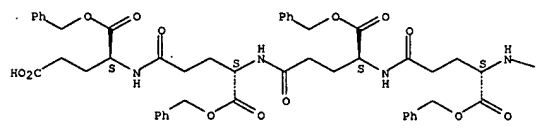
RN 112400-12-1 CAPLUS

CN L-Glutamic acid, N-[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, 1,1',1'',1''',1'''',1'''''-hexakis(phenylmethyl) ester (9CI) (CA INDEX NAME)

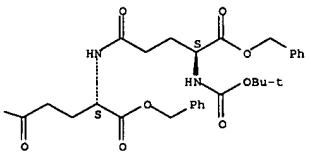
Absolute stereochemistry.

L6 ANSWER 108 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



PAGE 1-B



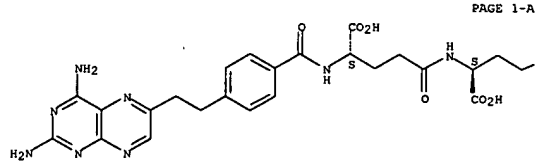
IT **105099-96-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and antifolate activity of)

RN 105099-96-5 CAPLUS

CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

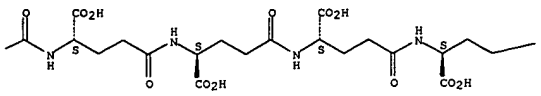
Absolute stereochemistry.

PAGE 1-A



L6 ANSWER 108 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B

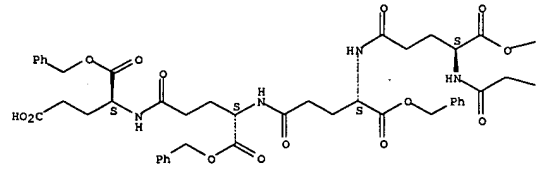


PAGE 1-C

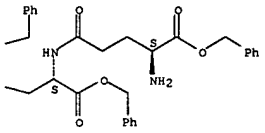
IT **112400-13-2DP**, resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and coupling of, with aminopteroic acid analogs)
RN 112400-13-2 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-(N-L-.gamma.-glutamyl-L-.gamma.-glutamyl)-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, 1,1',1'',1''',1'''',1'''''-hexakis(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

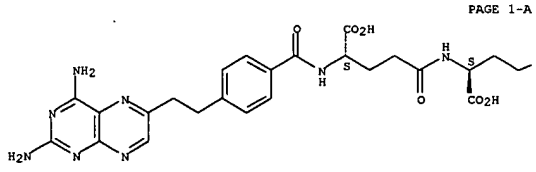


L6 ANSWER 108 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

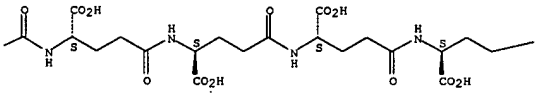
IT **112400-18-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 112400-18-7 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, monoammonium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 1-C

L6 ANSWER 109 OF 120 CAPLUS COPYRIGHT 2003 ACS

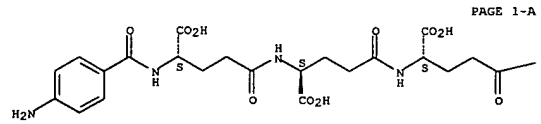
AB A new series of compds. that inhibit the polymn. of deoxyHb S by noncovalent interaction were studied. They consist of 3 structural elements: p-aminobenzoyl residue to anchor the compd. in the central cavity between the .beta. chains, a no. of glutamates in .gamma. linkage to provide tight binding, and one or two hydrophobic amino acid residues which block the intermol. hydrophobic interaction of valine .beta.6. The most active compd. was p-aminobenzoyl-(.gamma.-Glu)5-Phe-Phe. It increases the soly. of deoxy-HbS by a factor of 1.3 at a concn. of only 5-6 mM and is effective even in the presence of physiol. concns. of 2,3-diphosphoglycerate. Structure-activity relations are discussed.

ACCESSION NUMBER: 1988:48711 CAPLUS
DOCUMENT NUMBER: 108:48711
TITLE: p-Aminobenzoylpolyglutamates with hydrophobic end groups. A new class of inhibitors of hemoglobin S polymerization
AUTHOR(S): Benesch, Ruth E.; Kwong, Suzanna; Hudson, Barbara B.; Krumdieck, Carlos L.
CORPORATE SOURCE: Dep. Biochem. Mol. Biophys., Columbia Univ., New York, NY, 10032, USA
SOURCE: Journal of Biological Chemistry (1988), 263(1), 69-71
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

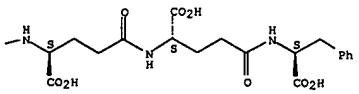
IT **111810-28-7 111810-31-2**
RL: BIOL (Biological study)
(Hb S polymn. inhibition by, structure in relation to)
RN 111810-28-7 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N-[N-(4-aminobenzoyl)-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

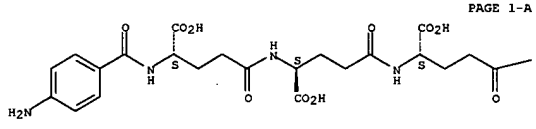


RN 111810-31-2 CAPLUS
CN L-Phenylalanine, N-[N-[N-[N-[N-[N-(4-aminobenzoyl)-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

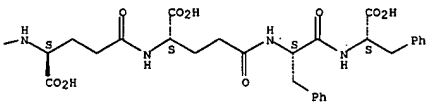
L6 ANSWER 109 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L6 ANSWER 110 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB The inhibition of dihydrofolate reductase (DHFR) of human breast cancer cells by metholrexate (I), 7-hydroxy-I, and various polyglutamates of I and 7-hydroxy-I was examd. I and its polyglutamates were the most potent inhibitors (ki = 1.7 .times. 10-10-0.5 .times. 10-10M); 7-hydroxy-I, formyldihydrofolate, and their tetra- and pentaglutamates, resp., were 100-500-fold less potent than I or its polyglutamates. Polyglutamylation of I or 7-hydroxy-I resulted in only modest increase in their inhibitory effects; polyglutamylation of formyldihydrofolate, however, markedly enhanced the effect of these compd. or DHFR. These observations are relevant to mechanism by which I inhibits DHFR and is therefore cyclotoxic to tumor cells.

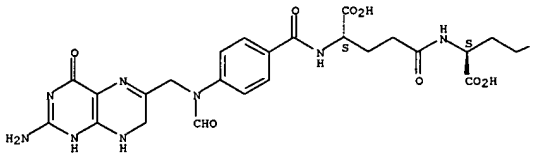
ACCESSION NUMBER: 1987:546917 CAPLUS
DOCUMENT NUMBER: 107:146917
TITLE: Effects on dihydrofolate reductase of methotrexate metabolites and intracellular folates formed following methotrexate exposure of human breast cancer cells
AUTHOR(S): Drake, James C.; Allegra, Carmen J.; Baram, Jacob; Kaufman, Bernard T.; Chabner, Bruce A.
CORPORATE SOURCE: Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Biochemical Pharmacology (1987), 36(14), 2416-18
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **110469-43-7**
RL: BIOL (Biological study)
(dihydrofolate reductase of human breast cancer cell inhibition by, polyglutamation in relation to)

RN 110469-43-7 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[[(2-amino-1,4,7,8-tetrahydro-4-oxo-6-pteridinyl)methyl]formylamino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-{9CI} (CA INDEX NAME)

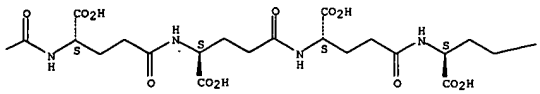
Absolute stereochemistry.

PAGE 1-A



L6 ANSWER 110 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B



PAGE 1-C

—CO_2H

L6 ANSWER 111 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB The cofactor content of various methanogenic bacteria was analyzed by HPLC techniques. In general there is a difference in cofactor compn. between hydrogenotrophic and methylotrophic methanogens. The former are characterized by the presence of methanopterin and coenzyme F423-2, while the latter contain sarcinapterin and coenzyme F420-4 and F420-5.

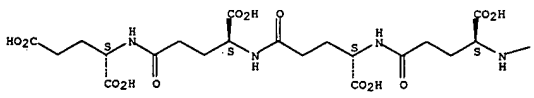
ACCESSION NUMBER: 1987:210634 CAPLUS
DOCUMENT NUMBER: 106:210634
TITLE: Methanogenic cofactors in pure cultures of methanogens in relation to substrate utilization
AUTHOR(S): Gorris, L. G. M.; Van der Drift, C.
CORPORATE SOURCE: Fac. Sci., Univ. Nijmegen, Nijmegen, NL-6525 ED, Neth.
SOURCE: Progress in Biotechnology (1986), 2(Biol. Anaerobic Bact.), 144-50
CODEN: PBITE3; ISSN: 0921-0423
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **108260-38-4**
RL: BIOL (Biological study)
(of methanogenic bacteria, substrate utilization in relation to)

RN 108260-38-4 CAPLUS
CN L-Glutamic acid, N-[(2S)-1-oxo-2-(phosphonooxy)propyl]-L-.gamma.-glutamyl-L-.gamma.-glutamyl-L-.gamma.-glutamyl-L-.gamma.-glutamyl-, P.fwdarw.5-ester with 1-deoxy-1-(3,4-dihydro-8-hydroxy-2,4-dioxopyrimido[4,5-b]quinolin-10(2H)-yl)-D-ribitol (9CI) (CA INDEX NAME)

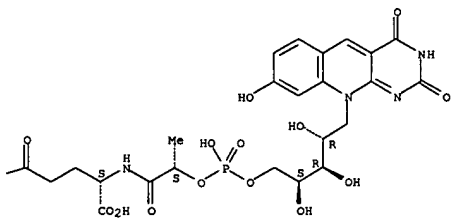
Absolute stereochemistry.

PAGE 1-A

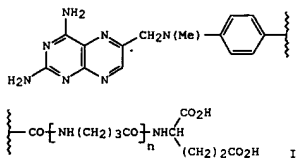


L6 ANSWER 111 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B



L6 ANSWER 112 OF 120 CAPLUS COPYRIGHT 2003 ACS
GI



I

AB Methotrexate polyglutamates I (n = 1-5) were prepd. and evaluated as inhibitors of dihydrofolate reductase (DHFR) [91425-22-8] and thymidylate synthase (TS) [9031-61-2] and as inhibitors of tumor cell growth in culture. With increasing chain length, I were less potent inhibitors of DHFR from murine leukemia cells (L1210) and showed decreased cytotoxicity. I showed variable effects on TS from L1210 cells and Lactobacillus casei. Structure-activity relations are discussed.

ACCESSION NUMBER: 1987:113125 CAPLUS
DOCUMENT NUMBER: 106:113125
TITLE: Inhibition of dihydrofolate reductase and thymidylate synthase by methotrexate polyglutamate analogs lacking "internal" .alpha.-carboxyl groups
AUTHOR(S): Rosowsky, A.; Forsch, R. A.; Wick, M. M.; Freisheim, J. H.; Danenberg, P. V.; Kalman, T. I.
CORPORATE SOURCE: Dana-Farber Cancer Inst., Boston, MA, 02115, USA
SOURCE: Chem. Biol. Pteridines, 1986, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.:
Chem., Biol. Clin. Aspects, 8th (1986), 985-8. Editor(s): Cooper, Bernard A.; Whitehead, V. Michael. de Gruyter: Berlin, Fed. Rep. Ger.
CODEN: 55HGAH
DOCUMENT TYPE: Conference
LANGUAGE: English

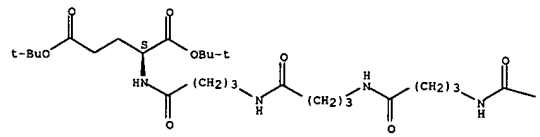
IT **107052-64-2**
RL: BIOL (Biological study)
(condensation of, with aminodeoxymethylpteroic acid)

RN 107052-64-2 CAPLUS
CN L-Glutamic acid, N-(24-amino-1,6,11,16,21-pentaoxo-5,10,15,20-tetraazatetracos-1-yl)-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

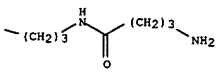
Absolute stereochemistry.

L6 ANSWER 112 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



PAGE 1-B



L6 ANSWER 113 OF 120 CAPLUS COPYRIGHT 2003 ACS
AB The effect of polyglutamylation (Glu2-Glu6) on the inhibitory potency of methotrexate (I) [59-05-2], 10-deazaaminopterin (II) [52454-37-2], and 10-ethyl-10-deazaaminopterin (III) [80576-83-6] for potential target enzymes was studied. Polygutamylation enhanced the inhibitory potency of the 3 antifolates for Lactobacillus casei thymidylate synthase [9031-61-2] in the order: I > II > III. In comparing the inhibitory potency of polyglutamyl derivs. of I and II for sheep liver dihydrofolate reductase [9002-03-3], I polyglutamyl derivs. became more inhibitory as Glu residues were added, whereas the inhibitory pattern with II polyglutamyl derivs. was more complex. Polyglutamyl derivs. of I and III, each with a total of 5 Glu residues were tested for their ability to inhibit aminoimidazolecarboxamide ribonucleotide transformylase [9032-03-5] derived from L1210 cells. Polyglutamyl I was more inhibitory than polyglutamyl III. Thus, in evaluating the potential enzyme inhibition by antifolates in a given tissue, the polyglutamyl chain length of inhibitor and substrate as well as the particular antifolate involved must be considered.

ACCESSION NUMBER: 1987:78244 CAPLUS
DOCUMENT NUMBER: 106:78244
TITLE: The antifolate activity of poly-.gamma.-glutamyl derivatives of methotrexate, 10-deazaaminopterin and 10-ethyl-10-deazaaminopterin
AUTHOR(S): Kisliuk, R. L.; Gaumont, Y.; Kumar, P.; Nair, M. G.; Kaufman, B. T.
CORPORATE SOURCE: Dep. Biochem. Pharmacol., Tufts Univ., Boston, MA, 02111, USA
SOURCE: Chem. Biol. Pteridines, 1986, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.:
Chem., Biol. Clin. Aspects, 8th (1986), 989-92. Editor(s): Cooper, Bernard A.; Whitehead, V. Michael. de Gruyter: Berlin, Fed. Rep. Ger.
CODEN: 55HGAH
DOCUMENT TYPE: Conference
LANGUAGE: English

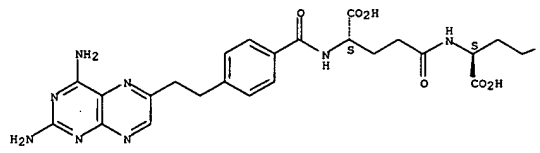
IT **105099-96-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antifolate activity of)

RN 105099-96-5 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

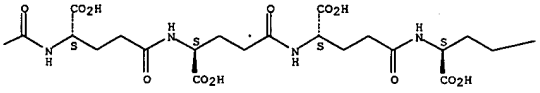
Absolute stereochemistry.

L6 ANSWER 113 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



PAGE 1-B



PAGE 1-C

L6 ANSWER 114 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB The specificity of hog liver folylpolyglutamate synthetase for folate substrates and for nucleotide and glutamate substrates and analogs was investigated. The kinetic mechanism, detd. by using aminopterin as the folate substrate, was ordered Ter-Ter with MgATP binding 1st, folate 2nd, and glutamate last. This mechanism precluded the sequential addn. of glutamate moieties to enzyme-bound folate. Folate, dihydrofolate, and tetrahydrofolate possessed the optimal configurations for catalysis (catalytic const. (kcat) = 2.5 s-1), whereas 5- and 10-position substitutions of the folate mol. impair catalysis. The kcat values decreased with increasing glutamate chain length, and the rate of decrease varied depending on the state of redn. and substitution of the folate mol. Folate binding, as assessed by on-rates, was slow. Dihydrofolate exhibited the fastest rate, and the rates were slightly reduced for tetrahydrofolate and 10-formyltetrahydrofolate and greatly reduced for 5-methyltetrahydrofolate and folic acid. The on-rates for most pteroyldiglutamates were similar to the rates for their resp. monoglutamate derivs., but further extension of the glutamate chain resulted in a progressive decrease in on-rates. Tetrahydrofolate polyglutamates were the only long glutamate chain length folates with detectable substrate activity. The specificity of the L-glutamate-binding site was very narrow. L-Homocysteate and 4-threo-fluoroglutamate were alternate substrates and acted as chain termination inhibitors in that their addn. to the folate mol. prevented or severely retarded the further addn. of glutamate moieties. The Km for glutamate was dependent on the folate substrate used. MgATP was the preferred nucleotide substrate, and .beta.,.gamma.-methylene-ATP, .beta.,.gamma.-imido-ATP, adenosine 5'-O-(3-thiotriphosphate), P1,P5-di(adenosine-5') pentaphosphate, and free ATP4- were potent inhibitors of the reaction.

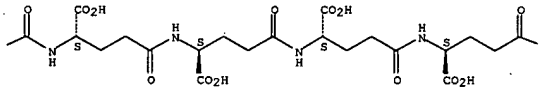
ACCESSION NUMBER: 1987:46382 CAPLUS
DOCUMENT NUMBER: 106:46382
TITLE: Mammalian folylpoly-.gamma.-glutamate synthetase. 2. Substrate specificity and kinetic properties
AUTHOR(S): Cichowicz, David J.; Shane, Barry
CORPORATE SOURCE: Sch. Hyg. Public Health, Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Biochemistry (1987), 26(2), 513-21
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **105816-61-3 105857-99-6**
RL: BIOL (Biological study)
(folylpolyglutamate synthetase of liver inhibition by, kinetics of)

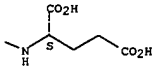
RN 105816-61-3 CAPLUS
CN L-Glutamic acid,
N-[N-[N-[N-[N-[N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, (S)- (9CI) (CA INDEX NAME)

L6 ANSWER 114 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B

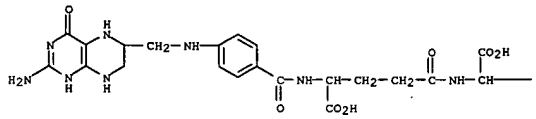


PAGE 1-C

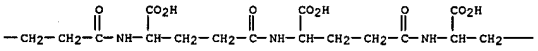


L6 ANSWER 114 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

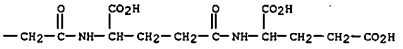
PAGE 1-A



PAGE 1-B



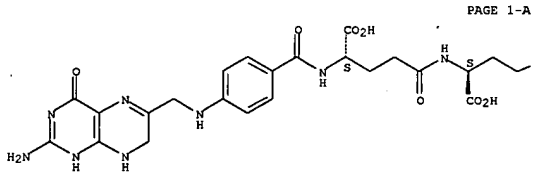
PAGE 1-C



RN 105857-99-6 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[N-[4-[[(2-amino-1,4,7,8-tetrahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



L6 ANSWER 115 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB The regulation of folate and folate analog metab. was studied in vitro by using purified hog liver folylpolyglutamate synthetase (I) as a model system and in vivo in cultured mammalian cells. The types of folylpolyglutamates that accumulate in vivo in hog liver, and changes in cellular folate levels and folylpolyglutamate distributions caused by physiol. and nutritional factors such as changes in growth rates and methionine, folate, and vitamin B12 status, can be mimicked in vitro by using purified enzyme. Folylpolyglutamate distributions can be explained solely in terms of the substrate specificity of I and can be modeled by using kinetic parameters obtained with purified enzyme. Low levels of I activity are normally required for the cellular metab. of folates to retainable polyglutamate forms, and consequently folate retention and concn., whereas higher levels of activity are required for the synthesis of the long-chain-length derivs. that are found in mammalian tissues. The synthesis of very-long-chain derivs., which requires tetrahydrofolate polyglutamates as substrates, is a very slow process in vivo. The slow metab. of 5-methyltetrahydrofolate to retainable polyglutamate forms causes the decreased tissue retention of folate in B12 deficiency. Although cellular folylpolyglutamate distributions change in response to nutritional and physiol. modulations, it is unlikely that these changes play a regulatory role in 1-C metab. as folate distributions respond only slowly. 4-Aminofolates are metabolized to retainable forms at a slow rate compared to folates. Although folate accumulation by cells is not very responsive to changes in I levels and cellular glutamate concns., cellular accumulation of anti-folate agents would be highly responsive to any factor that changes the expression of I activity.

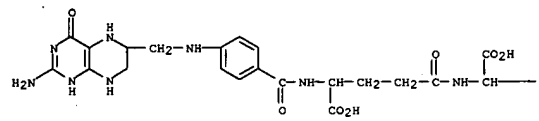
ACCESSION NUMBER: 1987:45819 CAPLUS
DOCUMENT NUMBER: 106:45819
TITLE: Mammalian folylpoly-.gamma.-glutamate synthetase. 4. In vitro and in vivo metabolism of folates and analogues and regulation of folate homeostasis
AUTHOR(S): Cook, Janine D.; Cichowicz, David J.; George, Sabu; Lawler, Ann; Shane, Barry
CORPORATE SOURCE: Sch. Hyg. Public Health, Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Biochemistry (1987), 26(2), 530-9
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **105816-61-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. of, by folylpolyglutamate synthetase)

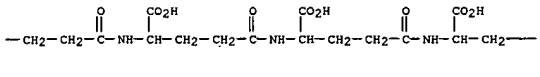
RN 105816-61-3 CAPLUS
CN L-Glutamic acid,
N-[N-[N-[N-[N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-, (S)- (9CI) (CA INDEX NAME)

L6 ANSWER 115 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

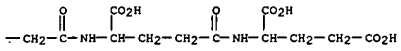
PAGE 1-A



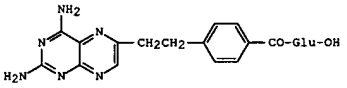
PAGE 1-B



PAGE 1-C



L6 ANSWER 116 OF 120 CAPLUS COPYRIGHT 2003 ACS
GI



I

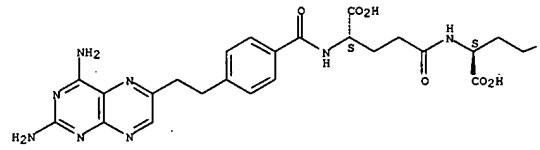
AB The actions of 10-deazaaminopterin (I) [52454-37-2], its 10-alkyl derivs., and their polyglutamates against thymidylate synthase (TMPS) [9031-61-2] from human acute myeloblastic leukemia were examd. Comparison of aminopterin [54-62-6] with methotrexate [59-05-2] showed that the methylation of the N10-position (methotrexate) increased the inhibitory effect of aminopterin on TMPS. In contrast, alkylation of the 10-position of 10-deazaaminopterin decreased inhibition of TMPS, and the 50% inhibitory concn. values were progressively higher in the 10,10-dimethyl- [80576-88-1], 10-methyl- [80576-77-8], and 10-ethyl- [80576-83-6] derivs. The addn. of .gamma.-glutamyl moieties of both 10-deazaaminopterin and one of its alkylated analogs, 10-ethyl-10-deazaaminopterin, enhanced inhibition. The max. inhibition was achieved with the addn. of 3 glutamyl moieties to 10-deazaaminopterin and 2 glutamyl moieties to 10-ethyl-10-deazaaminopterin, resp. Thus, 10-deazaaminopterin tetraglutamate [105099-92-1] was 130-fold and 10-ethyl-10-deazaaminopterin triglutamate [98984-63-5] was > 51-fold more active than their resp. parental compd. The compds. 10-deazaaminopterin and its polyglutamates, 10-methyl- and 10,10-dimethyl-analogs, inhibited TMPS in a noncompetitive fashion with respect to 5,10-methylene-tetrahydropteroylglutamate [3432-99-3]. In contrast, 10-ethyl-10-deazaaminopterin and its polyglutamates inhibited TMPS in a competitive fashion. With 5,10-methylene-tetrahydropteroylpentaglutamate [52768-21-5] as a substrate, 10-deazaaminopterin and its polyglutamates behaved as mixed-type inhibitors, and 10-ethyl-10-deazaaminopterin, monoglutamate [98984-61-3], and diglutamate [98984-62-4] behaved as noncompetitive inhibitors, whereas its pentaglutamate [**105100-00-3**] behaved as a mixed-type inhibitor. These results suggest that the addn. of .gamma.-glutamyl moieties to the substrate also caused the change in the mode of inhibitory action of these compds. These findings also show that both replacement of the N10-position of the 4-aminopteroyl structure with a methylene group and its alkylation caused interesting and unexpected changes in the structure-activity relationships and the mode of action for these 4-aminopteroyl antifolates as inhibitors of TMPS, which may be therapeutically relevant.

ACCESSION NUMBER: 1987:164 CAPLUS
DOCUMENT NUMBER: 106:164
TITLE: Inhibitory action of 10-deazaaminopterins and their polyglutamates on human thymidylate synthase
AUTHOR(S): Ueda, Takanori; Dutschman, Ginger E.; Nair, Madhavan G.; Degraw, Joseph I.; Sirotnak, Francis M.; Cheng, Yung Chi
CORPORATE SOURCE: Sch. Med., Univ. North Carolina, Chapel Hill, NC, 27514, USA

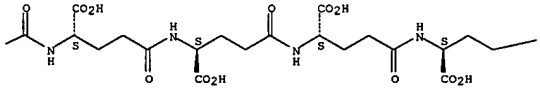
L6 ANSWER 116 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)
SOURCE: Molecular Pharmacology (1986), 30(2), 149-53
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **105099-96-5 105099-97-6 105100-00-3**
RL: BIOL (Biological study)
(thymidylate synthetase of human inhibition by, structure in relation to)
RN 105099-96-5 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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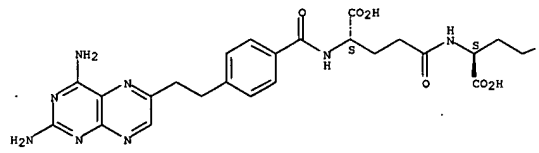
RN 105099-97-6 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

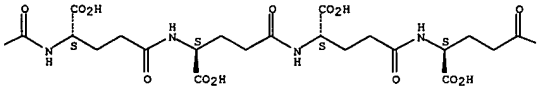
Absolute stereochemistry.

L6 ANSWER 116 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



PAGE 1-B



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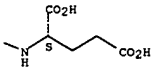
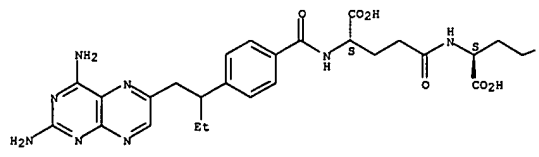


RN 105100-00-3 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[N-[4-[1-[(2,4-diamino-6-pteridinyl)methyl]propyl]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

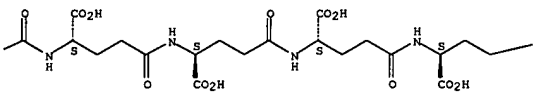
Absolute stereochemistry.

PAGE 1-A



L6 ANSWER 116 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B



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L6 ANSWER 117 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB Lubricating oil detergents and fuel (esp. gasoline) deposit inhibitors-detergents are prepd. by the reaction (at 100-175.degree.) of .gtoreq.1 C10-20 fatty acids, .gtoreq.1 C12-26-alkyl or -alkenylsuccinic acid or anhydride, and .gtoreq.1 polyalkylenepolyamine of formula RNH(R1NH)xH (R = C1-5-hydrocarbyl, R1 = C1-5-alkylene, x = 1-9). The additives are present at 0.00001-0.1 wt.% concn. in a fuel and at 1.0-5.0 wt.% concn. in a lubricating oil. The reaction is carried out with the fatty acids constituting 30-90 wt.% of the total acids (i.e., acids + anhydride) and with enough polyamine so that .apprx.40% of the available amino groups are reacted. Thus, tetraethylenepentamine 1.0, tall oil fatty acids 2.5, and C18-24-alkenylsuccinic anhydride 0.25 mol were reacted at 175.degree. to produce a product which, when present at 5.0 lbs/1000 bbl concn. in a gasoline, reduced carburetor deposits by 85% compared with the base fuel.

ACCESSION NUMBER: 1986:517956 CAPLUS
DOCUMENT NUMBER: 105:117956
TITLE: Compounds containing amide linkages from mono- and polycarboxylic acids in the same molecule and lubricants and fuels containing them
INVENTOR(S): Andress, Harry John; Ashjian, Henry; Gawel, Henry Anthony
PATENT ASSIGNEE(S): Mobil Oil Corp., USA
SOURCE: Eur. Pat. Appl., 6 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 186473	A2	19860702	EP 1985-309350	19851220
EP 186473	A3	19870513		
R: BE, DE, FR, GB, IT, NL				
CA 1247598	A1	19881227	CA 1985-496944	19851205
AU 8551001	A1	19860703	AU 1985-51001	19851209
AU 577906	B2	19881006		
BR 8506526	A	19860909	BR 1985-6526	19851226
ES 550418	A1	19870301	ES 1985-550418	19851226

PRIORITY APPLN. INFO.: US 1984-686776 19841227

IT **104235-49-6D**, reaction products with fatty acids and alkenylsuccinic acid
RL: USES (Uses)
(gasoline deposit inhibitors-detergents)
RN 104235-49-6 CAPLUS
CN 5,10,15,20,25,30,35,40-Octaazatetratetracontane-1,44-diamine (9CI) (CA INDEX NAME)

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L6 ANSWER 117 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

L6 ANSWER 118 OF 120 CAPLUS COPYRIGHT 2003 ACS

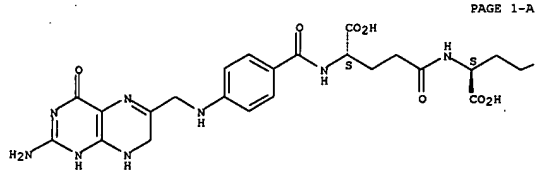
AB Dihydrofolate (I) and dihydropteroylpolyglutamates (DHPG) inhibited pig liver methylenetetrahydrofolate reductase (MTFR). In all cases the inhibition was linearly competitive with respect to methylene tetrahydrofolate. The Ki values decreased with each addnl. glutamyl residue from 1 to 6, from a value of 6.5 .mu.M for I to 0.013 .mu.M for dihydropteroylhexaglutamate (DHPHexG). Dihydropteroylheptaglutamate had a Ki of 0.065 .mu.M. These data indicated a free energy of binding of .apprx.0.75 kcal/mol for each of the 5 terminal glutamyl residues in DHPHexG. Methylenetetrahydropteroylpolyglutamates (MTHPPolG) were substrates for the enzyme, and the increased free energy of binding was reflected in increased values for Vmax/Km with polyglutamate substrates. The Vmax increased 1.76-fold on going from the mono- to the diglutamate substrate; addnl. glutamyl residues led to decreases in Km values for MTHPPolG. Evidently the in vivo activity of MTFR may also be sensitive to fluctuations in the ratio of MTHPPolG to DHPG. This ratio may be important in detg. the relative fluxes of MTHPPolG into the pathways leading to thymidylate biosynthesis and methionine regeneration.

ACCESSION NUMBER: 1980:421442 CAPLUS
DOCUMENT NUMBER: 93:21442
TITLE: Interactions of pig liver methylenetetrahydrofolate reductase with methylenetetrahydropteroylpolyglutamate substrates and with dihydropteroylpolyglutamate inhibitors
AUTHOR(S): Matthews, Rowena G.; Baugh, Charles M.
CORPORATE SOURCE: Biophys. Res. Div., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Biochemistry (1980), 19(10), 2040-5
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **105857-99-6**
RL: BIOL (Biological study)
(methylenetetrahydrofolate reductase inhibition by, kinetics of)
RN 105857-99-6 CAPLUS
CN L-Glutamic acid, N-[N-[N-[N-[N-[N-[4-[[(2-amino-1,4,7,8-tetrahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

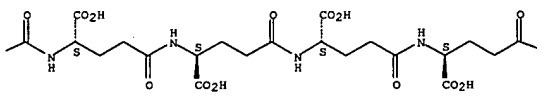
Absolute stereochemistry.

PAGE 1-A

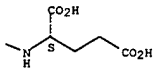


L6 ANSWER 118 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B



PAGE 1-C



L6 ANSWER 119 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB The Km and Vmax. values were detd. for dihydropteroyl glutamates with dihydrofolate reductases from 4 types of mammalian cell, and for methyltetrahydropteroylglutamates with a partially purified brain methionine synthetase. The mono- and oligoglutamates are probably utilized by the same enzyme form. Exponential-phase L5178Y mouse leukemia cells contained 5-methyltetrahydropteroyl penta-, -hexa-, and -hepta-glutamates; the di- but not the triglutamate was tentatively identified. Stationary-phase cells contained mostly the folate di-, tri-, penta-, and hexaglutamate forms, 5-methyltetrahydropteroylpentaglutamate being predominant.

ACCESSION NUMBER: 1977:85279 CAPLUS
DOCUMENT NUMBER: 86:85279
TITLE: Polyglutamate forms of folate: natural occurrence and role as substrates in mammalian cells
AUTHOR(S): Bertino, J. R.; Coward, J. K.; Cashmore, A.; Chello, P.; Panichajakul, S.; Horvath, C. G.; Stout, R. W.
CORPORATE SOURCE: Sch. Med., Yale Univ., New Haven, CT, USA
SOURCE: Biochemical Society Transactions (1976), 4(5), 853-6
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English

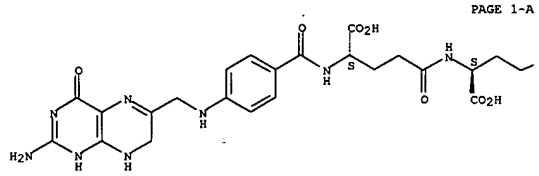
IT **105857-99-6**
RL: BIOL (Biological study)
(as dihydrofolate reductase substrate)

RN 105857-99-6 CAPLUS

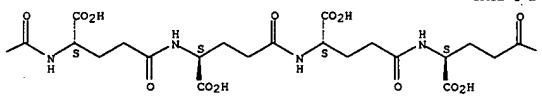
CN L-Glutamic acid, N-[N-[N-[N-[N-[N-[4-[[(2-amino-1,4,7,8-tetrahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

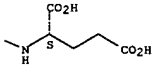


PAGE 1-B



L6 ANSWER 119 OF 120 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-C



L6 ANSWER 120 OF 120 CAPLUS COPYRIGHT 2003 ACS

AB The synthesis of 7,8-dihydropteroyl tri-, penta-, and heptaglutamate was accomplished by std. soln. peptide coupling, followed by dithionite redn. of the pterin moiety. These compds. were tested as substrates for dihydrofolate reductase (EC 1.5.1.3) obtained in highly purified form from 4 mammalian cell types: human acute myelogenous and acute lymphocytic leukemia cells, a methotrexate-resistant murine L1210 leukemia, and erythrocytes from a patient with polycythemia vera treated with methotrexate. In general, the dihydropolyglutamates were as good as or better substrates(lower Km, higher Vmax) than the corresponding monoglutamate forms. These data strengthen the concept that folate polyglutamates may be the naturally occurring coenzymes in mammalian tissues.

ACCESSION NUMBER: 1974:547551 CAPLUS
DOCUMENT NUMBER: 81:147551
TITLE: 7,8-Dihydropteroyl oligo-.gamma.-L-glutamates. Synthesis and kinetic studies with purified dihydrofolate reductase from mammalian sources
AUTHOR(S): Coward, James K.; Parameswaran, K. N.; Cashmore, Arlene R.; Bertino, Joseph R.
CORPORATE SOURCE: Sch. Med., Yale Univ., New Haven, CT, USA
SOURCE: Biochemistry (1974), 13(19), 3899-903
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

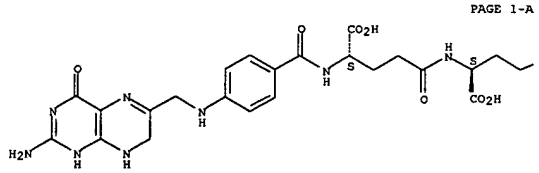
IT **105857-99-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with dihydrofolate reductase of mammal)

RN 105857-99-6 CAPLUS

CN L-Glutamic acid, N-[N-[N-[N-[N-[N-[4-[[(2-amino-1,4,7,8-tetrahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]-L-.gamma.-glutamyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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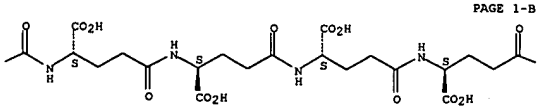

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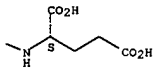

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         96.51     253.51

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                        -13.67     -14.32

FILE 'REGISTRY' ENTERED AT 17:34:41 ON 14 JUL 2003
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STRUCTURE FILE UPDATES:   13 JUL 2003  HIGHEST RN 547695-13-6
DICTIONARY FILE UPDATES:  13 JUL 2003  HIGHEST RN 547695-13-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

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Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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L7      STRUCTURE UPLOADED

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L7              STR
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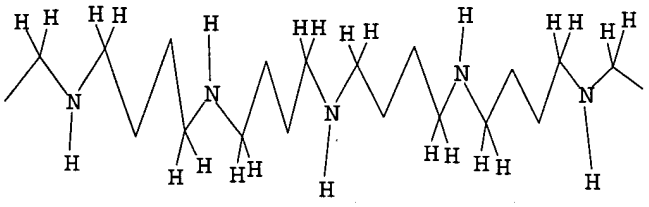

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Structure attributes must be viewed using STN Express query preparation.


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SAMPLE SCREEN SEARCH COMPLETED -  22323 TO ITERATE

  4.5% PROCESSED    1000 ITERATIONS                              0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01
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FULL FILE PROJECTIONS:  ONLINE   **INCOMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:       437534 TO   455386
PROJECTED ANSWERS:               0 TO        0

L8            0 SEA SSS SAM L7

=>
Uploading 09560711.str

L9      STRUCTURE UPLOADED

=> d query
L9                STR
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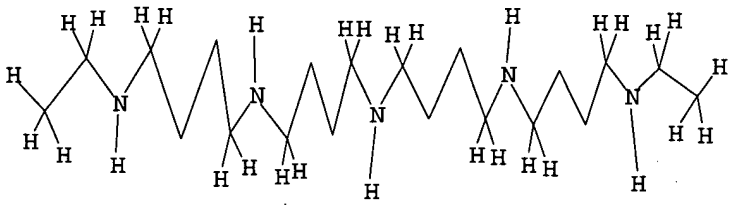

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Structure attributes must be viewed using STN Express query preparation.


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  4.5% PROCESSED    1000 ITERATIONS                                0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE   **INCOMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:       437534 TO   455386
PROJECTED ANSWERS:               0 TO        0

L10           0 SEA SSS SAM L9

=> s l9 full
FULL SEARCH INITIATED 17:35:50 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 445356 TO ITERATE

 89.8% PROCESSED  400000 ITERATIONS                               2 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.05

FULL FILE PROJECTIONS:  ONLINE   **INCOMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:       445356 TO   445356
PROJECTED ANSWERS:               2 TO        6

L11           2 SEA SSS FUL L9

=> fil caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
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FULL ESTIMATED COST 148.55 402.06

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE ENTRY TOTAL SESSION

CA SUBSCRIBER PRICE 0.00 -14.32

FILE 'CAPLUS' ENTERED AT 17:36:00 ON 14 JUL 2003
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FILE COVERS 1907 - 14 Jul 2003 VOL 139 ISS 3
FILE LAST UPDATED: 13 Jul 2003 (20030713/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l11
L12 34 L11

=> d l12 25-34 abs ibib hitstr

L12 ANSWER 25 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The naturally occurring polyamine spermine induces Hb synthesis in murine erythroleukemia (MEL) cells. We have studied the ability of various polyamine analogs to inhibit cell growth and induce Hb prodn. Polyamine analogs with free terminal amino groups were good inducers of Hb prodn. in MEL cells. Hb levels correlated with the no. of pos. charges: pentamines (five pos. charges) were stronger inducers than tetramines (four pos. charges). Compds. ethylated at their terminal amines were poor inducers of Hb prodn. but good inhibitors of MEL cell growth. These results provide evidence that polyamine analogs support specific biol. functions of polyamines in MEL cells and suggest relationships between polyamine structure and function.

ACCESSION NUMBER: 1995:728083 CAPLUS
DOCUMENT NUMBER: 123:165886
TITLE: The structure of polyamine analogs determines hemoglobin production and cytotoxicity in murine erythroleukemia cells
AUTHOR(S): Clement, Sophie; Delcros, Jean-Guy; Basu, Hirak S.; Quash, Gerard; Marton, Laurence J.; Feuerstein, Burt G.
CORPORATE SOURCE: Lab. d'Immunochim., Fac. Med. Lyon Sud., Oullins, 69921, Fr.
SOURCE: Biochemical Journal (1995), 309(3), 787-91
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(the structure of polyamine analogs dets. Hb prodn. and cytotoxicity in murine erythroleukemia cells)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

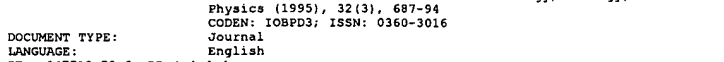
L12 ANSWER 26 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB These preclin. studies were carried out to examine the potential of the antiproliferative polyamine analog 1,19-bis-(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4) to serve as a therapy adjuvant to radiation for patients with rapidly dividing tumors of the head and neck (H&N). Cytostatic and cytotoxic effects of this polyamine analog were investigated in three squamous cell carcinoma (SCC) cell lines derived from human H&N tumors. Growth inhibition was achieved in all cell lines within 3-4 days of continuous 10 .mu.M drug exposure, and inhibition of cell cycle proliferation kinetics was confirmed via flow cytometry. Cytotoxicity was pronounced (3-4 log cell kill) in the SCC-38 and SCC-4Y cell lines with continuous 10 .mu.M analog exposure over 5 days, and was minimal in the SCC-13Y cell line. No demonstrable effect of BE-4-4-4-4 on single dose radiation survival was identified in any SCC cell line. Ornithine decarboxylase (ODC) activity was rapidly inhibited (1-2 h) following 10 .mu.M BE-4-4-4-4 exposure in all SCC cell lines (.apprx.90%), whereas identical exposure to 10 .mu.M difluoromethylornithine (DFMO) induced minimal ODC inhibition (.apprx.10%). Dose-dependent depletion of endogenous polyamines (putrescine, spermidine, spermine) was achieved in all SCC cell lines following 1 .mu.M and 10 .mu.M BE-4-4-4-4 exposures. Difluoromethylornithine was significantly less potent than BE-4-4-4-4 in its capacity to deplete endogenous polyamines, with no measureable depletion of spermine pools even with 5 mM .times. 48 h DFMO exposures. These data evaluate cytostatic and cytotoxic properties of the polyamine analog BE-4-4-4-4 in human SCCs, and suggest a role for investigation of such agents as an adjuvant to radiation in the therapeutic approach to rapidly dividing human tumors such as those that occur in the H&N.

ACCESSION NUMBER: 1995:681204 CAPLUS
DOCUMENT NUMBER: 123:102165
TITLE: Slowing proliferation in head and neck tumors: in vitro growth inhibitory effects of the polyamine analog BE-4-4-4-4 in human squamous cell carcinomas
AUTHOR(S): Harari, Paul M.; Pickart, Michael A.; Contreras, Lorenzo; Petereit, Daniel G.; Basu, Hirak S.; Marton, Laurence J.
CORPORATE SOURCE: School of Medicine, University of Wisconsin, Madison, WI, USA
SOURCE: International Journal of Radiation Oncology, Biology, Physics (1995), 32(3), 687-94
CODEN: IOBPD3; ISSN: 0360-3016
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE-4-4-4-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor effects of polyamine analog BE-4-4-4-4 in human head squamous-cell carcinomas)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)



L12 ANSWER 27 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Among over 60 polyamine derivs. tested, only N-(3-aminopropyl)octanediamine and bis-(3-aminopropyl)nonanediamine (TE 393) markedly inhibited [3H](+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801) binding at equil. in the presence of added spermidine (SPD) in non-washed rat brain synaptic membranes, without affecting that in the absence of added SPD. Although TE 393 significantly potentiated [3H]MK-801 binding before equil. in the presence of L-glutamic acid (Glu) alone or both Glu and glycine (Gly) added in Triton-treated membranes, the putative polyamine antagonists 1,10-decanediamine (DA10) and arcaine invariably inhibited binding irresp. of the addn. of agonists. In the absence of added SPD, in addn., TE 393 markedly enhanced abilities of both Glu and Gly to potentiate [3H]MK-801 binding before equil. However, TE 393 induced a rightward shift of the concn.-response curve of SPD for [3H]MK-801 binding before equil. Moreover, TE 393 was effective in potentiating binding of an antagonist but not an agonist radioligand to the NMDA domain and in inhibiting binding of an antagonist but not an agonist radioligand to the Gly domain. The potentiation of NMDA antagonist binding by TE 393 occurred in a manner sensitive to prevention by arcaine but not by DA10. TE 393 may be a novel ligand at the polyamine domain with an ability to interact with both the NMDA and Gly recognition domains in antagonist-preferring forms.

ACCESSION NUMBER: 1995:554182 CAPLUS
DOCUMENT NUMBER: 122:306683
TITLE: Search for novel ligands selective at a polyamine recognition domain on the N-methyl-D-aspartate receptor complex using membrane binding techniques
AUTHOR(S): Yoneda, Yukio; Ogita, Kiyokazu; Enomoto, Riyo; Kojima, Sumiko; Shuto, Makoto; Shirahata, Akira; Samejima, Keijiro
CORPORATE SOURCE: Department of Pharmacology, Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka, 573-01, Japan
SOURCE: Brain Research (1995), 679(1), 15-24
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(ligands selective at polyamine recognition domain on NMDA receptor complex)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

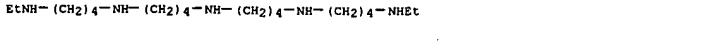
L12 ANSWER 28 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The polyamine spermine has both stimulatory and inhibitory effects on N-methyl-D-aspartate (NMDA) receptors. At recombinant NMDA receptors, effects of spermine are dependent on the subunit compn. of the receptor. In the present work we have used voltage-clamp recording to examine the effects of polyamines and bis(ethyl)polyamines on recombinant NMDA receptors expressed in Xenopus oocytes. The compds. that were studied include several bis(ethyl)polyamines that may be clin. useful as antitumor agents. A no. of pentaamines and bis(ethyl)pentaamines were found to act as potent voltage-dependent antagonists at heteromeric NR1A/NR2A and NR1A/NR2B receptors, but not at NR1A/NR2C receptors. Antagonism was more pronounced in oocytes voltage-clamped at -80 mV than at -20 mV. Some polyamine analogs also potentiated responses to glutamate at NR1A/NR2B receptors at membrane potentials of -20 to +40 mV, but this effect required higher concns. of polyamines than did inhibition seen at hyperpolarized membrane potentials. At NR1A/NR2A receptors the block seen with pentaamines and bis(ethyl)pentaamines, but not with spermine or bis(ethyl)spermine, was maximal at a membranes potential of -100 mV and was relieved at more neg. as well as at more pos. membrane potentials. This suggests that the mechanism of inhibition of NMDA receptors by pentaamines is different from that of spermine. Pentaamines may permeate the ion channel of NMDA receptors at very hyperpolarized membrane potentials and may be useful for studying the structural properties of NMDA receptor channels.

ACCESSION NUMBER: 1995:439716 CAPLUS
DOCUMENT NUMBER: 122:205814
TITLE: Antagonist properties of polyamines and bis(ethyl)polyamines at N-methyl-D-aspartate receptors
AUTHOR(S): Igarashi, Kazuei; Williams, Keith
CORPORATE SOURCE: Dep. Pharmacol., Univ. Pennsylvania Sch. Med., Philadelphia, PA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1995), 272(3), 1101-9
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **161811-51-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamines and bis(ethyl)polyamines as NMDA receptor antagonists)

RN 161811-51-4 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]-, pentahydrochloride (9CI) (CA INDEX NAME)



L12 ANSWER 28 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)

L12 ANSWER 29 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB N-Bisalkylpolyamine analogs have been shown to exert antiproliferative effects in many tumor models, with the bisethylderivs. exerting the greatest activities. 15N NMR spectroscopy was used to explore the interactions between these analogs and tRNA. When tRNA was added to solns. of 15N-enriched homospermine (4-4-4), bisethylhomospermine (BE-4-4-4), bismethylhomospermine (BM-4-4-4), bisethylspermine (BE-3-4-3) and 1,19-bis(ethylamino)-5,10,15-triazonadecane(BE-4-4-4-4), the spin-lattice relaxation times T1 of the nitrogens were strongly reduced. From the temp. dependence of these T1's we calcd. the rotational activation energies (Ea) of the correlation times of the amino groups in the presence and absence of tRNA. These data indicate that: i. the N-bisethyl derivs. bind strongly to tRNA through their NH2+-groups (most likely, through hydrogen bonding); ii. the binding is weakest in the N-bismethyl deriv. and iii. homospermine binds very weakly and mainly through its -NH3+-group (most likely, through electrostatic binding). The binding of the polyamine analogs to tRNA was also estd. by the increase of the half-line widths (D1/2) of the -NH2+-groups, derived from the effects that tRNA has on the spin-spin relaxation time T2.the decrease of the .nu.1/2 values of the-NH2+-groups in the (15N-polyamine)-tRNA complexes when the analogs were chased away by an excess of spermine confirmed the stronger binder of the bisethyl- with respect to the bismethyl derivs., as well as the weak binding of homospermine to tRNA. A correlation was also found between the binding strengths of the analyzed polyamine analogs and their antiproliferative activities.

ACCESSION NUMBER: 1995:140584 CAPLUS
DOCUMENT NUMBER: 122:177663
TITLE: Interactions between polyamine analogs with antiproliferative effects and tRNA: a 15N NMR analysis
AUTHOR(S): Fernandez, Claudio O.; Frydman, Benjamin; Samejima, Keijiro
CORPORATE SOURCE: Facultad Farmacia Bioquimica, Universidad Buenos Aires, Buenos Aires, 1113, Argent.
SOURCE: Cellular and Molecular Biology (Paris) (1994), 40(7), 933-44
CODEN: CMOBEF; ISSN: 0145-5680
PUBLISHER: C.M.B. Association
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamine analogs binding to tRNA in relation to antitumor activity and structure)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

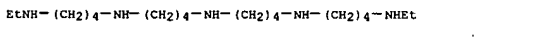
L12 ANSWER 30 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB We studied whether pretreatment of U-251 MG human brain tumor cells with the polyamine analog 1,19-bis(ethylamino)-5,1-,15-triazonadecane (BE-4-4-4-4) affected the cytotoxicity of the topoisomerase II inhibitor etoposide. We found that BE-4-4-4-4 protected cells from the cytotoxic effects of etoposide. Possible mechanisms for this protection may be related to enhanced DNA-nuclear matrix assocn. in analog-treated cells.

ACCESSION NUMBER: 1994:671550 CAPLUS
DOCUMENT NUMBER: 121:271550
TITLE: Pretreatment with the polyamine analog 1,19-bis(ethylamino)-5,10,15-triazonadecane (BE-4-4-4-4) inhibits etoposide cytotoxicity in U-251 MG (NCI) human brain tumor cells
AUTHOR(S): Smirnov, Ivan V.; Feuerstein, Burt G.; Pellarin, Malgorzata; Marton, Laurence J.; Deen, Dennis F.; Basu, Hirak S.
CORPORATE SOURCE: School Medicine, University California, San Francisco, CA, 94143, USA
SOURCE: Cellular and Molecular Biology (Paris) (1994), 40(7), 975-80
CODEN: CMOBEF; ISSN: 0145-5680
PUBLISHER: C.M.B. Association
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE-4-4-4-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BE-4-4-4-4 interaction with etoposide in human brain tumor cells)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)



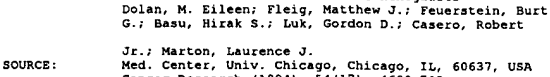
L12 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The polyamine analog 1,19-bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4), 5 mg/kg i.p., was given twice daily on days 0-3 and 7-10 (cycle 1) to nude mice with human malignant gliomas (SF-767 and U-87 MG), lung adenocarcinoma (A549), and colon carcinomas (HCT116 and HT29). A second cycle of drug was given to mice with SF-767 and A549 tumors on days 42-45 and 49-52. The max. animal wt. loss varied between 4 and 12%, which was obsd. 10-15 days following the initiation of treatment, but no overt toxic reactions were noted. The SF-767 brain tumors were extremely responsive to BE-4-4-4-4 alone (3 of 8 complete regressions after 2 cycles); however, the growth of the U-87 MG brain tumor was only slightly inhibited by BE-4-4-4-4 treatment. There was significant inhibition of tumor growth after treatment with one cycle of BE-4-4-4-4 in animals carrying the A549, HCT116, and HT29 tumors. At day 73, the growth of the A549 tumor was inhibited by 78 and 89% following one or two cycles of BE-4-4-4-4, resp. The mitotic index of A549 tumors was 18 times greater in control mice than in those treated with BE-4-4-4-4 for one or two cycles 99 days after initiation of treatment. 1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU) was given to mice carrying the U-87 MG or A549 tumors on day 4 (cycle 1) and day 46 (cycle 2) in the maximal tolerated dose of 50 mg/kg for BCNU alone and 40 mg/kg for BCNU plus BE-4-4-4-4. BCNU alone significantly inhibited the growth of U-87 MG tumors but not the growth of A549 tumors. Treatment with the combination of BCNU and BE-4-4-4-4 was significantly better than BCNU alone for A549 tumors and better than BE-4-4-4-4 alone for U87 tumors. However, in both animal groups treated with the combination, there was a significant wt. loss, which was not obsd. for animals treated with either agent alone. These data suggest a role for BE-4-4-4-4 in the treatment of brain, lung, and colon tumors.

ACCESSION NUMBER: 1994:570032 CAPLUS
DOCUMENT NUMBER: 121:170032
TITLE: Effect of 1,19-bis(ethylamino)-5,10,15-triazanonadecane on human tumor xenografts
AUTHOR(S): Dolan, M. Eileen; Fleig, Matthew J.; Feuerstein, Burt G.; Basu, Hirak S.; Luk, Gordon D.; Casero, Robert A., Jr.; Marton, Laurence J.
CORPORATE SOURCE: Med. Center, Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: Cancer Research (1994), 54(17), 4698-702
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE 4-4-4-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of, in human brain and lung and colon tumor xenografts)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)



L12 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)

L12 ANSWER 32 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The antiproliferating effect of nine kinds of bis(ethyl)polyamide analogs [three kinds each of bis(ethyl)triamine, bis(ethyl)tetraamine and bis(ethyl)pentaamine] was compared using FM3A (mouse mammary carcinoma) cells. The inhibitory effect was in the order BE4444 > BE3443 > BE4334 .gtoreq. BE444 > BE343 > BE333 ≥ BE44 > BE34 > BD33. The authors' results indicate that not only polyamine deficiency but also the accumulation of polyamine analogs is involved in the inhibition of cell growth. Accumulation of bis(ethyl)polyamine analogs caused the inhibition of protein synthesis and the decrease in the ATP content. The protein synthetic system in mitochondria was more strongly inhibited by bis(ethyl)polyamine analogs than that in the cytoplasm. Under conditions such that cytoplasmic protein synthesis was inhibited by 50% by bis(ethyl)polyamine analogs, mitochondrial protein synthesis was almost completely inhibited. Mitochondrial Ile-tRNA formation was inhibited by bis(ethyl)polyamine analogs at the concns. that cytoplasmic Ile-tRNA formation was stimulated. This may be one of the reasons for the selective inhibition of mitochondrial protein synthesis. This inhibition was followed by the decrease in ATP content, swelling of mitochondria and depletion of mitochondrial DNA. These results suggest that the early event of metabolic change caused by bis(ethyl)polyamine analogs in cells is the inhibition of protein synthesis, esp. of mitochondrial protein synthesis.

ACCESSION NUMBER: 1994:499157 CAPLUS
DOCUMENT NUMBER: 121:99157
TITLE: Correlation between the inhibition of cell growth by bis(ethyl)polyamine analogs and the decrease in the function of mitochondria
AUTHOR(S): He, Yong; Suzuki, Toshikazu; Kashiwagi, Keiko; Kusama-Eguchi, Kuniko; Shirahata, Akira; Igarashi, Kazuei
CORPORATE SOURCE: Fac. Pharm. Sci., Chiba Univ., Japan
SOURCE: European Journal of Biochemistry (1994), 221(1), 391-8
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE 4444
RL: BIOL (Biological study)
(mammary carcinoma cell growth inhibition by, mitochondrial function inhibition in relation to)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 33 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Computer graphics modeling and physicochem. studies of spermine-DNA interactions, as well as expts. in cell culture, indicate that a polyamine analog with strong affinity for nucleic acids but poor ability to condense and aggregate DNA in vitro should act as an antiproliferative agent if it can enter cells. On the basis of the their studies of polyamine-DNA interactions, the authors designed a pentamine, 1,19-bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4), that had these characteristics. Measurement of melting temp. and UV light scattering studies show that the affinity of this analog for calf-thymus DNA is about 4 times higher than that of spermine, whereas its ability to aggregate DNA is slightly poorer than that of spermine. Studies in U-87 MG, U-251 MG, SF-126, SF-188, SF-763, SF-767, and DAOY human brain tumor cells in tissue culture showed that treatment for more than 96 h with concns. of .gtoreq.5 .mu.M BE-4-4-4-4 inhibited growth; decreased levels of putrescine, spermidine, and spermine; and decreased colony-forming ability in all cell lines. The cytotoxicity of the analog varied among cell lines; DAOY and SF-767 were the most sensitive and the most resistant lines, resp. In SF-763 cells, growth inhibition by BE-4-4-4-4 could be partially reversed by the addn. of putrescine, spermidine, or spermine 1 day after BE-4-4-4-4 addn., but in U-251 MG cells, growth inhibition was reversed only by spermine and not by other polyamines. When any of the naturally occurring polyamines was added simultaneously with BE-4-4-4-4, growth inhibition was completely blocked. The data suggest that a threshold intracellular concn. of BE-4-4-4-4 is needed to manifest the growth-inhibitory and cytotoxic effects. In most cell lines, once that threshold level is reached, the growth-inhibitory and cytotoxic properties of the analog are manifest irresp. of cellular polyamine levels. Further increases in the BE-4-4-4-4 concn. or incubation time reduce the intracellular polyamine levels but do not increase growth inhibition. In U-87 MG and DAOY cells, however, prolonged incubation with higher concns. of BE-4-4-4-4 causes addnl. growth inhibition along with depletion of intracellular polyamines. Thus, it appears that polyamine analogs having higher affinity for DNA than natural polyamines can inhibit cell growth even in the presence of natural polyamines, if they are taken up by cells to a sufficient degree to compete with and displace natural polyamines from their binding sites on DNA.

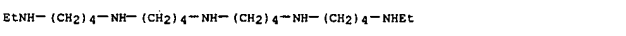
ACCESSION NUMBER: 1994:193 CAPLUS
DOCUMENT NUMBER: 120:193
TITLE: Interaction of a polyamine analog, 1,19-bis-(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4), with DNA and effect on growth, survival, and polyamine levels in seven human brain tumor cell lines
AUTHOR(S): Basu, Hirak S.; Pellarin, Malgorzata; Feuerstein, Burt G.; Shirahata, Akira; Samejima, Keijiro; Deen, Dennis F.; Marton, Laurence J.
CORPORATE SOURCE: Sch. Med., Univ. California, San Francisco, CA, 94143, USA

L12 ANSWER 33 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)

SOURCE: Cancer Research (1993), 53(17), 3948-55
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE 4-4-4-4
RL: BIOL (Biological study)
(brain neoplasm growth inhibition by, in human)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)



L12 ANSWER 34 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The interaction of spermine and polyamine analogs with synthetic polynucleotides of various base sequences complexed with ethidium bromide (EB) were investigated using measurements of fluorescence intensity and steady-state fluorescence polarization. Spermine and polyamine analogs displaced some but not all of the EB bound to poly(dA-dT).cntdot.poly(dA-dT) or poly(dG-dC).cntdot.poly(dG-dC), suggesting that polyamines may stabilize these polynucleotides in a conformation with reduced affinity for EB. Modifications of the aliph. backbone of spermine have pronounced effects on its ability to displace EB from poly(dA-dT).cntdot.poly(dA-dT) but not from poly(dG-dC).cntdot.poly(dG-dC). Spermine and some but not all of the polyamine analogs caused fluorescence depolarization when they interacted with the complex of EB and poly(dA-dT).cntdot.poly(dA-dT). Neither spermine nor any of the analogs, however, induced fluorescence depolarization in the complex of EB with poly(dG-dC).cntdot.poly(dG-dC) or poly(dA).cntdot.poly(dT). This suggests that spermine and some spermine analogs induce structural changes specific to alternating A-T sequences.

ACCESSION NUMBER: 1993:228426 CAPLUS
DOCUMENT NUMBER: 118:228426
TITLE: Differential effects of spermine and its analogs on the structures of polynucleotides complexed with ethidium bromide
AUTHOR(S): Delcros, Jean Guy; Sturkenboom, Miriam C. J. M.; Basu, Hirak S.; Shafer, Richard H.; Szollosi, Janos; Feuerstein, Burt G.; Marton, Laurence J.
CORPORATE SOURCE: Sch. Med., Univ. California, San Francisco, CA, 94143, USA
SOURCE: Biochemical Journal (1993), 291(1), 269-74
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **147510-59-6**
RL: PRP (Properties)
(DNA conformation response to, sequence specificity of)
RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

=> d l12 1-25 abs ibib hitstr

L12 ANSWER 1 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The invention provides methods and compns. for modulating polyamine pathway activity as a means for ameliorating neurodegenerative disorders. In particular, a method is provided for ameliorating the symptoms or onset of amyotrophic lateral sclerosis (ALS) by modulating the gene and protein products involved the polyamine pathway, e.g. by inhibiting the enzyme, ornithine decarboxylase, involved in the synthesis of the polyamine, putrescine. Compns. and methods are disclosed for inhibiting the polyamine pathway producing lower polyamine levels resulting in a beneficial effect on ALS. This can be accomplished by using modulating agents such as analogs, or polyamine analogs, and antiproliferative drugs. Screening assays for pharmacol. agents that are capable of decreasing polyamine levels and/or reducing cell proliferation are also disclosed.

ACCESSION NUMBER: 2003:417608 CAPLUS
DOCUMENT NUMBER: 138:396239
TITLE: Treatment of neurodegenerative disorders through the modulation of the polyamine pathway
INVENTOR(S): Tennore, Ramesh M.; Scott, Sean
PATENT ASSIGNEE(S): ALS Therapy Development Foundation, Inc., USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003043616	A2	20030530	WO 2002-US35203	20021101
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003130357	A1	20030710	US 2002-286042	20021101
US 2003130350	A1	20030710	US 2002-286604	20021101

PRIORITY APPLN. INFO.: US 2001-333263P P 20011116
OTHER SOURCE(S): MARPAT 138:396239

IT **147510-59-6**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamine pathway modulators for treatment of neurodegenerative disorders)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 2 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The polyamines spermidine and spermine and their diamine precursor putrescine are essential for mammalian cell growth and viability, and strategies are sought for reducing polyamine levels in order to inhibit cancer growth. Several structural analogs of the polyamines have been found to decrease natural polyamine levels and inhibit cell growth, probably by stimulating normal feedback mechanisms. In the present study, a large selection of spermine analogs has been tested for their effectiveness in inducing the prodn. of antizyme, a key protein in feedback inhibition of putrescine synthesis and cellular polyamine uptake. Bisethylnorspermine, bisethylhomospermine, 1,19-bis-(ethylamino)-5,10,15-triazanonadecane, longer oligoamine constructs and many conformationally constrained analogs of these compds. were found to stimulate antizyme synthesis to different levels in rat liver HTC cells, with some producing far more antizyme than the natural polyamine spermine. Uptake of the tested compds. was found to be dependent on, and limited by, the polyamine transport system, for which all these have approx. equal affinity. These analogs differed in their ability to inhibit HTC cell growth during 3 days of exposure, and this ability correlated with their antizyme-inducing potential. This is the first direct evidence that antizyme is induced by several polyamine analogs. Selection of analogs with this potential may be an effective strategy for maximizing polyamine deprivation and growth inhibition.

ACCESSION NUMBER: 2002:795681 CAPLUS
DOCUMENT NUMBER: 138:297219
TITLE: Antizyme induction by polyamine analogues as a factor of cell growth inhibition
AUTHOR(S): Mitchell, John L. A.; Leyser, Aviva; Holtorff, Michelle S.; Bates, Jill S.; Frydman, Benjamin; Valasinas, Aldonia L.; Reddy, Venodhar K.; Marton, Laurence J.
CORPORATE SOURCE: Department of Biological Sciences, Northern Illinois University, DeKalb, IL, 60115, USA
SOURCE: Biochemical Journal (2002), 366(2), 663-671
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE-4-4-4-4
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of and antizyme induction by polyamine analogs as factors for cell growth inhibition)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Microsporidia are eukaryotic obligate intracellular protists that are emerging pathogens in immunocompromised hosts, such as patients with AIDS or patients who have undergone organ transplantation. We have demonstrated in vitro and in vivo that synthetic polyamine analogs are effective antimicrosporidial agents with a broad therapeutic window. CD8-knockout mice or nude mice infected with the microsporidian Encephalitozoon cuniculi were cured when they were treated with four different novel polyamine analogs at doses ranging from 1.25 to 5 mg/kg of body wt./day for a total of 10 days. Cured animals demonstrated no evidence of parasitemia by either PCR or histol. staining of tissues 30 days after untreated control animals died.

ACCESSION NUMBER: 2002:30291 CAPLUS
DOCUMENT NUMBER: 136:318859
TITLE: Novel synthetic polyamines are effective in the treatment of experimental microsporidiosis, an opportunistic AIDS-associated infection
AUTHOR(S): Bacchi, Cyrus J.; Weiss, Louis M.; Lane, Schenella; Frydman, Benjamin; Valasinas, Aldonia; Reddy, Venodhar; Sun, Jerry S.; Marton, Laurence J.; Khan, Imitiaz A.; Moretto, Magali; Yarlett, Nigel; Wittner, Murray
CORPORATE SOURCE: Haskins Laboratories and Departments of Biology and Chemistry, Pace University, New York, NY, 10038-1598, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2002), 46(1), 55-61
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, SL 11061
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel synthetic polyamines are effective in treatment of exptl. microsporidiosis, opportunistic AIDS-assocd. infection)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Polyamines are known to be involved in cell growth regulation in breast cancer. To evaluate the efficacy of bis(ethyl)polyamine analogs for breast cancer therapy and to understand their mechanism of action we measured the effects of a series of polyamine analogs on cell growth, activities of enzymes involved in polyamine metab., intracellular polyamine levels, and the uptake of putrescine and spermidine using MCF-7 breast cancer cells. The IC50 values for cell growth inhibition of three of the compds., N1,N12-bis(ethyl)spermine, N1,N11- bis(ethyl)norspermine, and N1,N14-bis(ethyl)homospermine, were in the range of 1-2 .mu.M. Another group of three compds. showed antiproliferative activity at about 5 .mu.M level. These compds. are also capable of suppressing colony formation in soft agar assay and inducing apoptosis of MCF-7 cells. The highly effective growth inhibitory agents altered the activity of polyamine biosynthetic and catabolic enzymes and down-regulated the transport of natural polyamines, although each compd. produced a unique pattern of alterations in these parameters. HPLC anal. showed that cellular uptake of bis(ethyl)polyamines was highest for bis(ethyl)spermine. We also analyzed polyamine analog conformations and their binding to DNA minor or major grooves by mol. modeling and mol. dynamics simulations. Results of these analyses indicate that tetramine analogs fit well in the minor groove of DNA whereas, larger compds. extend out of the minor groove. Although major groove binding was also possible for the short tetramine analogs, this interaction led to a predominantly bent conformation. Our studies show growth inhibitory activities of several potentially important analogs on breast cancer cells and indicate that multiple sites are involved in the mechanism of action of these analogs. While the activity of an analog may depend on the sum of these different effects, mol. modeling studies indicate a correlation between antiproliferative activity and stable interactions of the analogs with major or minor grooves of DNA.

ACCESSION NUMBER: 2000:675543 CAPLUS
DOCUMENT NUMBER: 133:329131
TITLE: Molecular correlates of the action of bis(ethyl)polyamines in breast cancer cell growth inhibition and apoptosis
AUTHOR(S): Faaland, Carol A.; Thomas, T. J.; Balabhadrapathruni, Srivani; Langer, Thierry; Mian, Somia; Shirahata, Akira; Gallo, Michael A.; Thomas, Thresia
CORPORATE SOURCE: Department of Environmental and Community Medicine, Environmental and Occupational Health Sciences Institute, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ, 08903, USA
SOURCE: Biochemistry and Cell Biology (2000), 78(4), 415-426
CODEN: BCBIEQ; ISSN: 0829-8211
PUBLISHER: National Research Council of Canada
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE-4-4-4-4
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mol. correlates of the action of bis(ethyl)polyamines in breast cancer cell growth inhibition and apoptosis)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 4 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)

EtNH—$(CH_2)_4$—NH—$(CH_2)_4$—NH—$(CH_2)_4$—NH—$(CH_2)_4$—NHEt

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 5 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The inefficient uptake of oligodeoxynucleotides, including that of TFO, through the cell membrane is a limiting factor in developing gene therapy approaches for cancer and other diseases. To develop a new strategy for oligonucleotide delivery into the nucleus, we synthesized a series of novel polyamine analogs and examd. their effects on the uptake of a 37-mer [32P]-labeled TFO, targeted to the promoter region of c-myc oncogene. We used MCF-7 breast cancer cells to investigate the efficacy of polyamines on the internalization of the TFO. The uptake of TFO was enhanced by complexing it with several unsubstituted polyamine analogs at 0.1-5-.mu.M concns., with up to 6-fold increase in TFO uptake in the presence of a hexamine, 1,21-diamino-4,9,13,18-tetraazahenicosane (H2N(CH2)3NH(CH2)4NH(CH2)3NH(CH2)4NH(CH2)3NH2 or 3-4-3-4-3). TFO uptake increased with the cationicity of the polyamines; however, bis(ethyl) substitution and structural features of the methylene bridging region had significant effects on TFO uptake. The majority of labeled TFO was recovered from the nuclear fraction contg. genomic DNA. Electrophoretic mobility shift assay revealed enhanced binding of TFO to a target duplex contg. promoter region sequence of c-myc oncogene. Treatment of MCF-7 cells with the TFO complexed with 0.5 .mu.M 3-4-3-4-3 suppressed c-myc mRNA level by 65%, as detd. by Northern blot anal. These data indicate a novel approach to deliver oligodeoxynucleotides to the cell nucleus, and suppress the expression of target genes, and provide new insights into the mechanism of oligonucleotide transport in living cells.

ACCESSION NUMBER: 1999:595840 CAPLUS
DOCUMENT NUMBER: 131:331729
TITLE: Facilitation of the Cellular Uptake of a Triplex-Forming Oligonucleotide by Novel Polyamine Analogues: Structure-Activity Relationships
AUTHOR(S): Thomas, Rajan M.; Thomas, Thresia; Wada, Makiko; Sigal, Leonard H.; Shirahata, Akira; Thomas, T. J.
CORPORATE SOURCE: Departments of Medicine Environmental and Community Medicine Pediatrics Molecular Genetics and Microbiology The Cancer Institute of New Jersey and the Environmental and Occupational Health Sciences Institute, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ, 08903, USA
SOURCE: Biochemistry (1999), 38(40), 13328-13337
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of polyamines on cellular uptake of triplex-forming oligonucleotide targeted to promoter region of c-myc oncogene in breast cancer)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

EtNH—$(CH_2)_4$—NH—$(CH_2)_4$—NH—$(CH_2)_4$—NH—$(CH_2)_4$—NHEt

L12 ANSWER 5 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 6 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Polyamines, casein kinase II (CKII), and the myc oncogene are directly involved in the regulation of mol. events in cell proliferation, differentiation, and apoptosis. Each is increased in rapidly growing cancer cells. In our current study, we showed that the Km values for purified CKII were similar for casein and Myc oncoprotein under a variety of assay conditions, and that specific natural and synthetic polyamines stimulated CKII phosphorylation of Myc oncoprotein 2- to 20-fold via increases in Vmax. When polyamine synthesis inhibitors and analogs were studied with this purified enzyme system, two polyamine analogs . (N1,N12-bis-(ethyl)-spermine [BESpm] and 1,19-bis-(ethylamino)-5,10,15, triazononadecane [BE4X4]), which did not affect basal enzyme activity, did prevent (or inhibit) polyamine-stimulated CKII activity by approx. 70 and 85 percent, resp. Because the Myc oncoprotein trans activates several genes for key proteins involved in the regulation of cellular proliferation, including the ornithine decarboxylase gene (rate-limiting enzyme of polyamine synthesis), we suggest that there may be linkages between polyamines, CKII, and Myc in the control of cellular proliferation. We also suggest that the anticancer drugs BESpm and BE4X4 may inhibit cancer cell proliferation partially through interference with the above-suggested CKII linkages.

ACCESSION NUMBER: 1999:400003 CAPLUS
DOCUMENT NUMBER: 131:179457
TITLE: Effects of polyamines, polyamine synthesis inhibitors, and polyamine analogs on casein kinase II using myc oncoprotein as substrate
AUTHOR(S): Gundogus-Ozcanli, Nesrin; Sayilir, Cafer; Criss, Wayne E.
CORPORATE SOURCE: Department of Medical Biology, Istanbul University Medical School, Istanbul, Turk.
SOURCE: Biochemical Pharmacology (1999), 58(2), 251-254
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamines, polyamine synthesis inhibitors, and polyamine analogs effect on CKII using myc oncoprotein as substrate)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

EtNH—$(CH_2)_4$—NH—$(CH_2)_4$—NH—$(CH_2)_4$—NH—$(CH_2)_4$—NHEt

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 7 OF 34 CAPLUS COPYRIGHT 2003 ACS
AB Unavailable
ACCESSION NUMBER: 1999:324015 CAPLUS
DOCUMENT NUMBER: 131:189813
TITLE: Mechanism of dansylation of the polyamine pentaazapentacosane pentahydrochloride
AUTHOR(S): Heimbecher, Susan Klara
CORPORATE SOURCE: Univ. of Arizona, Tucson, AZ, USA
SOURCE: (1998) 82 pp. Avail.: UMI, Order No. DA9901657 From: Diss. Abstr. Int., B 1999, 59(8), 4128
DOCUMENT TYPE: Dissertation
LANGUAGE: English
IT **147510-59-6**
RL: ANT (Analyte); RCT (Reactant); ANST (Analytical study); RACT (Reactant or reagent)
(mechanism of dansylation of polyamine pentaazapentacosane pentahydrochloride)
RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

IT **161811-51-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(mechanism of dansylation of polyamine pentaazapentacosane pentahydrochloride)
RN 161811-51-4 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]-, pentahydrochloride (9CI) (CA INDEX NAME)

L12 ANSWER 8 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)
therapeutic and diagnostic methods)
RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 8 OF 34 CAPLUS COPYRIGHT 2003 ACS
AB Methods for modulating macrophage proliferation in an individual afflicted
with or at risk for a macrophage-assocd. disease are provided. The methods employ a polyamine analog, or salt or protected deriv. thereof. Macrophage proliferation has been implicated in a no. of serious disorders, including AIDS (HIV)-assocd. dementia, AIDS-assocd. non-Hodgkin's lymphoma, and Alzheimer's disease. The invention also provides methods for aiding diagnosis and monitoring therapy of a macrophage-assocd. non-HIV assocd. dementia, esp. Alzheimer's disease. The invention also provides methods of delaying development of macrophage-assocd. non-HIV assocd. dementias, including Alzheimer's disease, which entail administration of an agent which modulates macrophage proliferation.
ACCESSION NUMBER: 1999:297292 CAPLUS
DOCUMENT NUMBER: 130:332882
TITLE: Methods for modulating macrophage proliferation using polyamine analogs, and therapeutic and diagnostic methods
INVENTOR(S): McGrath, Michael S.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9921542	A2	19990506	WO 1998-US22747	19981027
WO 9921542	A3	20000120		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2308274	AA	19990506	CA 1998-2308274	19981027
AU 9912018	A1	19990517	AU 1999-12018	19981027
AU 760546	B2	20030515		
EP 1027040	A2	20000816	EP 1998-955140	19981027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001520990	T2	20011106	JP 2000-517701	19981027

PRIORITY APPLN. INFO.: US 1997-63317P P 19971027
US 1997-63318P P 19971027
US 1998-179383 A2 19981026
WO 1998-US22747 W 19981027
OTHER SOURCE(S): MARPAT 130:332882
IT **147510-59-6 147510-59-6D**, protected derivs. and stereoisomers
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(polyamine analogs for modulating macrophage proliferation, and

L12 ANSWER 9 OF 34 CAPLUS COPYRIGHT 2003 ACS
AB The polyamine analog bis(ethyl-amino)-5,10,15-triazanonadecane (BE-4-4-4-4) depletes cellular polyamines and inhibits malignant cell growth. It was previously shown that BE-4-4-4-4 inhibits nucleosome condensation on supercoiled DNA in a cell-free system. It was sought to det. whether BE-4-4-4-4 inhibits nucleosome condensation in cells, and whether that effect alters the expression of specific genes. The simian virus 40 (SV-40) mini-chromosome was used as a model system and the expression of the viral late genes was studied. It is known that the SV-40 late genes are regulated by the steroid receptor elements that, in turn, control gene expression by altering nucleosomal organization. A more than 6-fold increase was obsd. in SV-40 late gene expression in cells
pretreated with BE-4-4-4-4 for 18 h. The polyamine analog bisethyl norspermine (BE-3-3-3), that does not affect nucleosomal condensation in cell free systems and has little effect on chromatin structure in cultured
human tumor cells, had a negligible effect on SV-40 late gene expression under treatment conditions identical to those used with BE-4-4-4-4. Similar to the findings in the cell-free system, the polyamine analog BE-4-4-4-4 inhibited nucleosome formation and, thereby, altered the expression of specific genes in a cellular system.
ACCESSION NUMBER: 1999:191817 CAPLUS
DOCUMENT NUMBER: 130:217813
TITLE: Polyamine analog bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4) enhances simian virus 40
late gene expression
AUTHOR(S): Basu, Hirak S.; Dreckschmidt, Nancy; Tu, Linh; Chanbusarakum, Lisa
CORPORATE SOURCE: Dep. Human Oncology, Univ. Wisconsin, Madison, WI, 53792, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1999), 43(4), 336-340
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **147510-59-6**, BE-4-4-4-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(polyamine analog BE-4-4-4-4 enhances SV-40 late gene expression)
RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The in vitro and in vivo sensitivity of N1,N11-di(ethyl)norspermine (DENSPM) and 1,19-di(ethylamino)-5,10,15-triazononadecane (BE-4-4-4-4) was investigated in prostate cancer cells. Colony-forming assays were performed utilizing rat prostate cancer cell lines AT3.1, AT6.1 and AT6.3, and the androgen-insensitive human prostate cancer cell lines DU145, DuPro-1 and TSU-Pr1. The antitumor activity of BE-4-4-4-4 was evaluated by treatment of DuPro-1 and PC-3 xenograft tumors in nude mice. BE-4-4-4-4 was 4-86 times more cytotoxic in clonogenic assays than DENSPM in both rat and human prostate carcinoma cell lines. BE-4-4-4-4 and DENSPM inhibited DuPro-1 tumors in animals. After treatment with therapeutic doses of BE-4-4-4-4, minimal to mild necrosis and inflammation was seen histopathol. in the kidneys on days 15 and 22. On day 35, regeneration of those cells was completed.

ACCESSION NUMBER: 1998:220103 CAPLUS
DOCUMENT NUMBER: 128:239138
TITLE: Effects of polyamine analogs on prostatic adenocarcinoma cells in vitro and in vivo
AUTHOR(S): Zagaja, Gregory P.; Shrivastav, Maneesh; Fleig, Matthew J.; Marton, Laurence J.; Rinker-Schaeffer, Carrie W.; Dolan, Eileen M.
CORPORATE SOURCE: Department Surgery, Section Urology, University Chicago, Chicago, IL, 60637, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1998), 41(6), 505-512
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE-4-4-4-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of polyamine analogs on prostatic adenocarcinoma cells)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 11 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The mechanism was elucidated by which polyamine analog-induced changes in DNA and chromatin may increase the cytotoxicity of cis-diaminedichloroplatinum (CDDP). Micrococcal nuclease sensitivity of the nuclei was studied and the amt. of Pt incorporated into the nucleosomal and linker regions of chromatin isolated from CDDP-treated U-251 MG human malignant brain tumor cells was measured. Pretreatment with the 2 cytotoxic polyamine analogs 1,11-bis(ethylamino)-4,8-diazaundecane and 1,19-bis(ethylamino)-5,10,15-diazanonadecane was carried out. Pretreatment of the cells with the polyamine analogs decreased the micrococcal nuclease sensitivity and increased the incorporation of CDDP preferentially into the linker region of the chromatin.

ACCESSION NUMBER: 1998:165574 CAPLUS
DOCUMENT NUMBER: 128:188320
TITLE: The mechanism of polyamine analog-induced enhancement of cisplatin cytotoxicity in the U-251 MG human malignant glioma cell line
AUTHOR(S): Paliwal, Jonathan; Janumpalli, Gita; Basu, Hirak S.
CORPORATE SOURCE: Department Human Oncology, Medical Science Center, Madison, WI, 53706, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1998), 41(5), 398-402
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE-4-4-4-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism of polyamine analog-induced enhancement of cisplatin cytotoxicity)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Dansylation of the pentaamine pentaazapentacosane .cntdot.5 HCl (PAPC) produces only the perdansyl product. This occurs even under conditions of pH and dansyl chloride concn. most likely to produce partially dansylated products. This result is explained by a mechanism whereby only completely unionized amine mols. will dansylate. The proposed mechanism is supported by the dansylation vs. pH profile of PAPC vs. that of a ref. monoamine (piperidine .cntdot.HCl). After 4 h at room temp. and pH 9.5, 100 of piperidine is dansylated while under the same conditions only 10 of PAPC is derivatized. A pH greater than 10.5 is required to completely dansylate PAPC. This difference is significantly greater than would be predicted from the pKa values but it is consistent with the proposed mechanism.

ACCESSION NUMBER: 1998:70415 CAPLUS
DOCUMENT NUMBER: 128:184577
TITLE: Mechanism of dansylation of the polyamine pentaazapentacosane-5 HCl
AUTHOR(S): Heimbecher, Susan; Lee, Yung-Chi; Tabibi, S. Esmail; Yalkowsky, Samuel H.
CORPORATE SOURCE: College of Pharmacy, Department of Pharmaceutical Sciences, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: International Journal of Pharmaceutics (1998), 160(1), 21-29
CODEN: IJPHDE; ISSN: 0378-5173
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **161811-51-4**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(mechanism of dansylation of the polyamine pentaazapentacosane-5HCl)

RN 161811-51-4 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]-, pentahydrochloride (9CI) (CA INDEX NAME)

●5 HCl

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

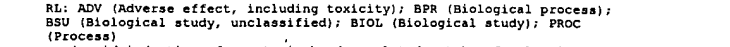
L12 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Treatment of Chinese hamster ovary cells with .alpha.-difluoromethylornithine for 3 days, followed by exposure to cycloheximide, led to an unregulated, rapid and massive accumulation of polyamine analogs. This accumulation led to cell death by apoptosis within a few hours. Clear evidence of DNA fragmentation was seen in response to both N-terminally ethylated polyamines and to polyamines contg. Me groups on the terminal carbon atoms. Programmed cell death was induced within 2-4 h of exposure to 1 .mu.M or higher concns. of N1,N11-bis(ethyl)norspermine. The presence of cycloheximide increased the uptake of the polyamine analogs and therefore led to cell death at lower analog concns., but it was not essential for the induction of apoptosis, since similar effects were seen when the protein synthesis inhibitor was omitted and the concn. of N1,N11-bis(ethyl)norspermine was increased to 5 .mu.M or more The induction of apoptosis was blocked both by the addn. of the caspase inhibitor N-benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone, or by the addn. of the polyamine oxidase inhibitor N1-methyl-N2-(2,3-butadienyl)butane-1,4-diamine (MDL 72,527). These expts. provide evidence to support the concepts that: (1) polyamines or their oxidn. products may be initiators of programmed cell death; (2) regulation of polyamine biosynthesis and uptake prevents the accumulation of toxic levels of polyamines; and (3) the antineoplastic effects of bis(ethyl) polyamine analogs may be due to the induction of apoptosis in sensitive tumor cells.

ACCESSION NUMBER: 1997:801517 CAPLUS
DOCUMENT NUMBER: 128:152313
TITLE: Rapid induction of apoptosis by deregulated uptake of polyamine analogs
AUTHOR(S): Hu, Rei-Huang; Pegg, Anthony E.
CORPORATE SOURCE: Departments of Cellular and Molecular Physiology and Pharmacology, M. S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, PA, 17033, USA
SOURCE: Biochemical Journal (1997), 328(1), 307-316
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE 4-4-4-4
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(rapid induction of apoptosis by deregulated uptake of polyamine analogs)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The formation and stability of triplex DNA were investigated in the presence of a no. of tetramine (+4) and pentamine (+5) derivs. of spermine with altered spacing between the pos. charges and bis(ethyl) substitution of pendant amino groups. Thermal denaturation profiles were measured for the duplex and triplex forms of poly[d(TC)].cntdot.poly[d(GA)] and poly(dA).cntdot.poly(dT); in both cases the pentamines were more effective than the tetramines in increasing the melting temp. (Tm) of the triplexes. Some structural effects were evident, although bisethylation of the polyamines had only a minor effect on the Tm of pyrimidine-purine-pyrimidine triplexes. Relative assocn. consts. to poly(dT).cntdot.poly(dA).cntdot.poly(dT) and poly[d(AT)] were measured by an ethidium competition assay. These results demonstrated tighter binding of the pentamines by a factor of up to 10-fold, but bisethylation consistently decreased the relative assocn. consts. to the triplex. A third assay involving transmol. triplex formation between sepd. pyrimidine-purine tracts in plasmid DNA was also employed. Again the pentamines promoted triplex formation at lower concns. than the tetramines but structural effects were very important in detg. the degree of triplex formation. These results may be important for the design of suitable ligands to stabilize triplex DNA in antigene therapeutics and to elucidate the mechanism of action of polyamine analogs as antitumor drugs.

ACCESSION NUMBER: 1997:770747 CAPLUS
DOCUMENT NUMBER: 128:124954
TITLE: Pyrimidine-purine-pyrimidine triplex DNA stabilization in the presence of tetramine and pentamine analogs of spermine
AUTHOR(S): Thomas, T. J.; Ashley, Carolyn; Thomas, Thresia; Shirahata, Akira; Sigal, Leonard H.; Lee, Jeremy S.
CORPORATE SOURCE: Department of Medicine, University of Medicine and Dentistry of New Jersey - Robert Wood Johnson Medical School, New Brunswick, NJ, 08903, USA
SOURCE: Biochemistry and Cell Biology (1997), 75(3), 207-215
CODEN: BCBIEQ; ISSN: 0829-8211
PUBLISHER: National Research Council of Canada
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pyrimidine-purine-pyrimidine triplex DNA stabilization in presence of tetramine and pentamine analogs of spermine)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 15 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB We describe a method for the profiling of polyamines, N-acetylated polyamines and the polyamine analogs N1,N11-bis(ethyl)norspermine (BE-3-3-3) and 1,19-bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4) in L1210 murine leukemia cells by capillary gas chromatog. with nitrogen-phosphorus detection. The method makes use of four internal stds. Prepurifn. comprises deproteinization, isolation with Sep-Pak silica at pH 9.0, conversion to heptafluorobutyryl derivs. and postderivatization org. fluid extn. Within- and between-series precisions (given as C.V.s) for anal. of 1-2.times.106 cells were: putrescine 5.5 and 29.4%; spermidine 1.6 and 7.1%; and spermine 3.2 and 7.6%, resp. Recoveries relative to the resp. internal std., were in the 70.6-104.7% range. Accuracy and precision of measurements of BE-4-4-4-4 can probably be improved by the introduction of a sep. pentamine internal std. We conclude that the method can be used for studying the effect of BE-3-3-3 and BE-4-4-4-4, and possibly their metabolites, on polyamine homeostasis (biosynthesis, retroconversion, transport, terminal catabolism) and polyamine function.

ACCESSION NUMBER: 1997:707391 CAPLUS
DOCUMENT NUMBER: 128:72463
TITLE: Simultaneous determination of polyamines, N-acetylated polyamines and the polyamine analogs BE-3-3-3 and BE-4-4-4-4 by capillary gas chromatography with nitrogen-phosphorus detection
AUTHOR(S): Dorhout, Bernard; Kingma, Anneke W.; de Hoog, Elly; Muskiet, Frits A. J.
CORPORATE SOURCE: Central Laboratory for Clinical Chemistry, University Hospital Groningen, P.O. Box 30.001, RB Groningen, 9700, Neth.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1997), 700(1 + 2), 23-30
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE-4-4-4-4
RL: ANT (Analyte); BOC (Biological occurrence); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence)
(simultaneous detn. of polyamines and analogs BE-3-3-3 and BE-4-4-4-4 by capillary gas chromatog.)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 16 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Polyamines are biol. cations necessary for normal cell growth. Polyamine analogs have been shown to be effective inhibitors of tumor growth. The effect of the polyamine analogs 1,19-bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4), N1,N11-bis(ethyl)norspermine (BE-3-3-3) and 1,15-bis(ethylamino)-4,12-diazapentadecane (BE-3-7-3) on the growth of the prostate cancer cell lines DU145, LNCaP and PC-3 was tested in vitro. The effect of BE-4-4-4-4 on androgen-independent DU145 cells in vivo via a nude mouse xenograft model was tested. In vivo, mice were given saline or BE-4-4-4-4 3 or 5 mg/kg i.p. twice daily on days (3 cycle). The proliferation of DU145, LNCaP and PC-3 prostate cancer cell lines was inhibited in a dose-dependent manner by BE-4-4-4-4. Intracellular putrescine, spermidine and spermine levels in all 3 cell lines declined after only 24 h exposure to BE-4-4-4-4 in vitro. Animals receiving BE-4-4-4-4 showed inhibition of tumor growth which continued throughout the expt. with 74 and 81% growth inhibition seen on day 101. No overt toxic reactions besides wt. loss were obsd. in BE-4-4-4-4 treated animals. Tumor tissue from animals treated with BE-4-4-4-4 showed a dose-dependent decrease in spermidine and spermine levels but no decline in putrescine levels as compared with control.

ACCESSION NUMBER: 1997:356263 CAPLUS
DOCUMENT NUMBER: 127:144913
TITLE: Effects of the polyamine analogs BE-4-4-4-4, BE-3-7-3, and BE-3-3-3 on the proliferation of three prostate cancer cell lines
AUTHOR(S): Jeffers, Lisa; Church, Dawn; Basu, Hirak; Marton, Laurence; Wilding, George
CORPORATE SOURCE: Comprehensive Cancer Center, University Wisconsin, Madison, WI, 53792, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1997), 40(2), 172-179
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**, BE-4-4-4-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamine analogs effects on the proliferation of three prostate cancer cell lines)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 17 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB A rapid HPLC method for detn. of the dansyl deriv. of pentaazapentacosane (PAPC)-5HCl was developed. The chromatog. system used a reversed-phase C8 column, a mobile phase of HOAc buffer and MeCN and UV detection. The dansylation conditions were optimized with a pH of 11.0 and a 20-fold dansyl chloride excess. The yield of dansyl-PAPC increased 10-fold as the reaction pH was changed from 9.5 to 10.5. Under derivatization conditions of pH 8.5-11.0 and 1-30-fold excess dansyl chloride only perdansyl PAPC was found.

ACCESSION NUMBER: 1997:156794 CAPLUS
DOCUMENT NUMBER: 126:255561
TITLE: Derivatization and high-performance liquid chromatographic analysis of pentaazapentacosane pentahydrochloride
AUTHOR(S): Heimbecher, Susan; Lee, Yung-Chi; Tabibi, S. Esmail; Yalkowsky, Samuel H.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, AZ, USA
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1997), 691(1), 173-178
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: ANT (Analyte); ANST (Analytical study)
(147510596; derivatization and HPLC detn. of pentaazapentacosane)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 18 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The natural polyamines, putrescine, spermidine, and spermine, are known to stabilize pyrimidine-purine-pyrimidine and purine-purine-pyrimidine triplex DNA formation. We studied the ability of two tetramine and two pentamine analogs of spermine and their bis(ethyl) derivs. to stabilize triplex DNA formation between 5'-TG3TG4TG4TG3T-3' and its target duplex probe, consisting of the oligonucleotides 5'-TCGAAG3AG4AG4AG3A-3' and 5'-TCGATC3TC4TC4TC3T-3'. We used electrophoretic mobility shift assay (EMSA), melting temp. (Tm) measurements, and CD spectroscopy to evaluate the effects of these novel polyamine analogs on triplex DNA stability, dissocn. consts., aggregation, and conformation. In general, pentamines were more efficacious than tetramines in stabilizing triplex DNA, although most of the polyamines with pendant free amino groups caused DNA aggregation below 50% conversion to triplex DNA. Et substitution of these pendant amino groups lowered their efficacy approx. 2-fold in stabilizing triplex DNA; however, this effect was more than compensated for by the lack of DNA aggregation in the presence of bis(ethyl)polyamines. A concn.-dependent increase in the Tm of triplex DNA was obsd. in the presence of polyamines. CD spectral measurements showed distinct differences in the conformation of triplex DNA stabilized in the presence of polyamines compared to the CD spectra of the oligonucleotides alone. Temp.-dependent CD spectra of triplex DNA showed monophasic melting in the absence and presence of polyamines, suggesting duplex/triplex .fwdarw. single-stranded DNA transition. These results indicate that structural modifications of polyamines is an effective strategy to develop triplex DNA-stabilizing ligands, with potential applications in anti-gene therapeutics.

ACCESSION NUMBER: 1997:105149 CAPLUS
DOCUMENT NUMBER: 126:141110
TITLE: Effects of Chain Length Modification and Bis(ethyl) Substitution of Spermine Analogs on Purine-Purine-Pyrimidine Triplex DNA Stabilization, Aggregation, and Conformational Transitions
AUTHOR(S): Musso, Marco; Thomas, Thresia; Shirahata, Akira; Sigal, Leonard H.; Van Dyke, Michael W.; Thomas, T. J.
CORPORATE SOURCE: Department of Tumor Biology, University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Biochemistry (1997), 36(6), 1441-1449
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: MSC (Miscellaneous); PRP (Properties)
(effects of chain length modification and bis(ethyl) substitution of spermine analogs on purine-purine-pyrimidine triplex DNA stabilization, aggregation, and conformational transitions)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 18 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)

L12 ANSWER 19 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB We investigated the effects of the polyamine spermine and 2 of its cytotoxic analogs 1,11-bis(ethyl-amino)-4,8-diazaundecane (BE-3-3-3) and 1,19-bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4) on the formation of nucleosomes on neg. and pos. supercoiled DNA in vitro. Histones H2A, H2B, H3, and H4 were reconstituted onto DNA to form nucleosomes and the polyamines were added either before or after histone addn. The structural state of the nucleosome was monitored by analyzing the DNA topoisomers that were present after topoisomerase I treatment. Although polyamines induced DNA aggregation to various degrees, high concns. of topoisomerase I were able to relax the aggregated DNA and the helical pitch was found to be unaltered in the aggregates. When histones were assocd. with neg. coiled DNA, the polyamine-induced aggregation did not alter nucleosome structure. The induced aggregate did inhibit nucleosomal transitions when examd. on pos. coiled DNA. BE-4-4-4-4 was most effective and BE-3-3-3 least effective. These analogs were also extremely effective in inhibiting histone deposition onto DNA. A potential mechanism for the action of these analogs is both to inhibit histone deposition during DNA replication and also disrupt nucleosomal dynamics due to aberrant chromatin condensation. These results also suggest that BE-4-4-4-4 and BE-3-3-3 may produce their cytotoxic effect through slightly different mechanisms.

ACCESSION NUMBER: 1997:101161 CAPLUS
DOCUMENT NUMBER: 126:289678
TITLE: Effects of spermine and its cytotoxic analogs on nucleosome formation on topologically stressed DNA in vitro
AUTHOR(S): Basu, Hirak S.; Smirnov, Ivan V.; Peng, Hong Fan; Tiffany, Karen; Jackson, Vaughn
CORPORATE SOURCE: Department Human Oncology, University Wisconsin, Madison, WI, 53706, USA
SOURCE: European Journal of Biochemistry (1997), 243(1/2), 247-258
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(spermine and its cytotoxic analogs effect on nucleosome formation on topol. stressed DNA)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 20 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB Therapeutic polyamines useful as cancer chemotherapeutic agents are disclosed which have formula R1NH(CH2)wNH(CH2)xNH(CH2)yNH(CH2)zNHR2 (R1, R2 = Cl-5 hydrocarbon chain; w, x, y, z = 1-10). One such mol. is N1,N19-bis(ethylamino)-5,10,15-triazanonadecane (I), which is longer than spermine. I may be used alone or in combination with other therapeutic agents such as 1,3-bis(2-chloroethyl)-1-nitrosourea or cisplatin. I·5HCl was prepd. by condensation of N-(p-tosyl)-N-ethyl-4-bromobutylamine (prepd. from tosylethylamine and 1,4-dibromobutane) with N1,N5,N9-tribenzyl-5-aza-1,9-diaminononane [prepd. from PhCH2NH2 and N-(4-bromobutyl)phthalimide], followed by reductive debenzylation. These compds. mimic natural polyamines in many of their metabolic interactions, but do not perform the polyamine functions needed to support cell growth and therefore disable these functions. Thus, I bound to DNA better than spermine, but did not impart the conformational changes in DNA caused by spermine which are required for cell growth. I was also not degraded by plasma polyamine oxidase.

ACCESSION NUMBER: 1996:494741 CAPLUS
DOCUMENT NUMBER: 125:185863
TITLE: Cancer therapeutic polyamines
INVENTOR(S): Basu, Hirak S.; Feuerstein, Burt; Marton, Laurence; Samejima, Keijiro
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 50 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5541230	A	19960730	US 1993-147527	19931105
US 5880161	A	19990309	US 1996-690648	19960729

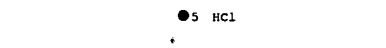
PRIORITY APPLN. INFO.: US 1993-147527 19931105
OTHER SOURCE(S): MARPAT 125:185863

IT **147510-59-6P 161811-51-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cancer therapeutic polyamines)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

RN 161811-51-4 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]-, pentahydrochloride (9CI) (CA INDEX NAME)

L12 ANSWER 20 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)



●5 HCl

L12 ANSWER 21 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The monoclonal antispermine antibody Spm8-2 was obtained by immunizing mice with a thyroglobulin-spermine conjugate. The mol. requirements for polyamines binding to this antibody were investigated by ELISA binding and inhibition tests, using a variety of natural polyamines and synthetic polyamine analogs. Four major structural determinants are important for the binding of polyamines by the antibody: (1) terminal amino groups: N-alkylation of both terminal amino groups of the polyamines leads to an important drop in the affinity for the antibody; (2) no. of methylene groups spacing the amino groups: the 4 carbon chains appear to present the optimum length since the antibody binds polyamines with repeats of the aminobutyl moiety more actively than their homologs with shorter or longer carbon chains; (3) no. of amino groups: the affinity of Spm8-2 for free homologous polyamines varied in the following order: pentamines > tetramines > triamines > diamines, showing the importance of the no. of pos. charges of the polyamines in the antibody-antigen reaction; the importance of charges is further emphasized by the dependence of antibody binding on the ionic strength of the medium; (4) N-acylation of one terminal amino group: the antibody binds more actively N1-acetylspermidine than spermidine or spermine. The binding properties of Spm8-2 suggest the presence of 2 recognition sequences, one selective for N-acylaminopropyl moieties, the second for the aminobutyl moiety.

ACCESSION NUMBER: 1996:489746 CAPLUS
DOCUMENT NUMBER: 125:165349
TITLE: Molecular requirements for polyamines binding to the antispermine monoclonal antibody Spm8-2
AUTHOR(S): Delcros, Jean-Guy; Clement, Sophie; Bouille, Nathalie; Royou, Anne; Debroise, Isabelle; Thomas, Vincent; Moulinoux, Jacques-Philippe
CORPORATE SOURCE: Faculte de Medecine Lyon Sud, Laboratoire d'Immunochimie INSERM C.J.F.89-05, Oullins, Fr.
SOURCE: Hybridoma (1996), 15(3), 177-183
CODEN: HYBRDY; ISSN: 0272-457X
PUBLISHER: Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **147510-59-6**, BE-4-4-4-4
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mol. requirements for polyamines binding to antispermine monoclonal antibody Spm8-2)
RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 22 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB We studied the effects of 72 h pretreatment with five polyamine analogs on the cytotoxicity of cis-diamminedichloroplatinum (II) (CDDP) in U-251 MG and SF-188 human brain tumor cells. A colony forming efficiency assay showed that the pretreatment with clin. important analogs 1,11-bis(ethylamino)-4,8-diazaundecane (BE-3-3-3), 1,14-bis(ethylamino)-5,10-diazatetradecane (BE-4-4-4), and 1,19-bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4) increased the cytotoxicity of CDDP by 1.3 to 2.3-fold; 1,19-diamino-5,10,15-triazanonadecane (4-4-4-4) did not affect CDDP cytotoxicity, and 1,11-diamino-4,8-diazaundecane (3-3-3) protected cells from the cytotoxic effects of CDDP. An alk. elution assay detected a small increase in DNA interstrand cross-links accompanying the enhancement of CDDP cytotoxicity only in cells pretreated with BE-3-3-3. This study is the first to show that the Z-DNA inducing abilities of the polyamine analogs in synthetic polynucleotides in vitro correlates inversely with their effects on CDDP cytotoxicity in human tumor cells in culture.

ACCESSION NUMBER: 1996:299271 CAPLUS
DOCUMENT NUMBER: 125:25724
TITLE: The ability of polyamine analogs to induce Z-DNA structure in synthetic polynucleotides in vitro inversely correlates with their effects on cytotoxicity of cis-diamminedichloroplatinum (II) (CDDP) in human brain tumor cell lines
AUTHOR(S): Basu, Hirak S.; Pellarin, Malgorzata; Feuerstein, Burt G.; Marton, Laurence J.
CORPORATE SOURCE: Department Human Oncology, University Wisconsin, Madison, WI, 53706, USA
SOURCE: Anticancer Research (1996), 16(1), 39-47
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamine analogs induce Z-DNA structure in polynucleotides in vitro and correlation with their effects on cytotoxicity of cisplatin in human brain tumor cell lines)
RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 23 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The pharmacokinetics of 1,19-bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4) were detd. in CD2F1 female mice after administration of i.v. bolus doses of 20 mg/kg (approx. the dose lethal to 10% of the study animals, .apprx. LD10) as well as 15, 10, and 5 mg/kg and after s.c., i.p., or p.o. doses of 20 mg/kg. BE-4-4-4-4 in plasma and urine was derivatized with dansyl chloride and measured by gradient high-performance liq. chromatog. (HPLC) with fluorescence detection. Data were modeled by noncompartmental and compartmental methods. The declines obsd. in plasma BE-4-4-4-4 concns. after i.v. delivery of 20, 15, 10, and 5 mg/kg were modeled simultaneously using an interval of 2000 min between doses and were best approximated by a two-compartment, open, linear model. The time courses of plasma BE-4-4-4-4 concns. after i.p. and s.c. delivery were fit best by a two-compartment, open, linear model with first-order absorption. Peak plasma concns. of BE-4-4-4-4 measured following an i.v. dose of 20 mg/kg ranged between 30 and 33 .mu.g/mL, the terminal elimination half-life was 94 min, and the vol. of distribution (Vdss) was 850 mL/kg. The plasma pharmacokinetics of BE-4-4-4-4 were linear with dose. BE-4-4-4-4 (0.5 and 2.0 .mu.M) in mouse plasma was approx. 67% protein-bound. Bioavailabilities after i.p., s.c., and p.o. delivery were 40%, 50%, and approx. 3%, resp. Urinary excretion of parent BE-4-4-4-4 in the first 24 h after dosing accounted for less than 30% of the delivered dose. As BE-4-4-4-4 proceeds toward and undergoes clin. evaluation, the data and anal. method presented herein should prove useful in formulating a dose-escalation strategy and, possibly, evaluating toxicities encountered.

ACCESSION NUMBER: 1996:283854 CAPLUS
DOCUMENT NUMBER: 125:223
TITLE: Plasma pharmacokinetics and urinary excretion of the polyamine analog 1,19-bis(ethylamino)-5,10,15-triazanonadecane in CD2F1 mice
AUTHOR(S): Eiseman, Julie L.; Yuan, Zhi-Min; Eddington, Natalie D.; Sentz, Dorothy L.; Callery, Patrick S.; Egorin, Merrill J.
CORPORATE SOURCE: Division of Developmental Therapeutics, University of Maryland Cancer Center, Baltimore, MD, 21201, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1996), 38(1), 13-20
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **147510-59-6**, BE-4-4-4-4
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(plasma pharmacokinetics and urinary excretion of polyamine analog bis(ethylamino)triazanonadecane in CD2F1 mice and detn. by HPLC)
RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 23 OF 34 CAPLUS COPYRIGHT 2003 ACS (Continued)

L12 ANSWER 24 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB 1,14-Bis(ethyl)amino-5,10-diazatetradecane N1,N11-bis(ethyl)norspermine (BE-4-4-4) and 1,19-bis(ethylamino)-5,10,15-triazanonadecane (BE-4-4-4-4) are 2 relatively new polyamine analogs synthesized for use as antineoplastic agents. In the human brain tumor cell lines U-251 MG and SF-767, both agents inhibited cell growth, were cytotoxic, induced a variable G1/S block, and depleted intracellular polyamines. Since intracellular polyamine depletion did not always correlate with growth inhibition, cell survival, or cell cycle progression, such depletion cannot completely explain the effects of these agents on growth, survival, and cell cycle progression in U-251 MG and SF-767 cells.

ACCESSION NUMBER: 1995:872803 CAPLUS
DOCUMENT NUMBER: 123:329467
TITLE: Two polyamine analogs (BE-4-4-4 and BE-4-4-4-4) directly affect growth, survival, and cell cycle progression in two human brain tumor cell lines
AUTHOR(S): Bergeron, Christophe J.; Basu, Hirak S.; Marton, Laurence J.; Deen, Dennis F.; Pellarin, Malgorzata; Feuerstein, Burt G.
CORPORATE SOURCE: School Medicine, University California, San Francisco, CA, 94143, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1995), 36(5), 411-17
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(polyamine analogs BE-4-4-4 and BE-4-4-4-4 effect on cell cycle, growth, and survival of human brain tumor)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

L12 ANSWER 25 OF 34 CAPLUS COPYRIGHT 2003 ACS

AB The naturally occurring polyamine spermine induces Hb synthesis in murine erythroleukemia (MEL) cells. We have studied the ability of various polyamine analogs to inhibit cell growth and induce Hb prodn. Polyamine analogs with free terminal amino groups were good inducers of Hb prodn. in MEL cells. Hb levels correlated with the no. of pos. charges: pentamines (five pos. charges) were stronger inducers than tetramines (four pos. charges). Compds. ethylated at their terminal amines were poor inducers of Hb prodn. but good inhibitors of MEL cell growth. These results provide evidence that polyamine analogs support specific biol. functions of polyamines in MEL cells and suggest relationships between polyamine structure and function.

ACCESSION NUMBER: 1995:728083 CAPLUS
DOCUMENT NUMBER: 123:165886
TITLE: The structure of polyamine analogs determines hemoglobin production and cytotoxicity in murine erythroleukemia cells
AUTHOR(S): Clement, Sophie; Delcros, Jean-Guy; Basu, Hirak S.; Quash, Gerard; Marton, Laurence J.; Feuerstein, Burt G.
CORPORATE SOURCE: Lab. d'Immunochim., Fac. Med. Lyon Sud., Oullins, 69921, Fr.
SOURCE: Biochemical Journal (1995), 309(3), 787-91
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **147510-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(the structure of polyamine analogs dets. Hb prodn. and cytotoxicity in murine erythroleukemia cells)

RN 147510-59-6 CAPLUS
CN 1,4-Butanediamine, N-[4-(ethylamino)butyl]-N'-[4-[[4-(ethylamino)butyl]amino]butyl]- (9CI) (CA INDEX NAME)

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	159.86	561.92

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-22.13	-36.45

FILE 'REGISTRY' ENTERED AT 17:39:48 ON 14 JUL 2003
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 13 JUL 2003 HIGHEST RN 547695-13-6
DICTIONARY FILE UPDATES: 13 JUL 2003 HIGHEST RN 547695-13-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

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FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
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PROJECTED ANSWERS:               0 TO        0

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FULL SCREEN SEARCH COMPLETED - 434805 TO ITERATE

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INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.05

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                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       434805 TO   434805
PROJECTED ANSWERS:               1 TO        4

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FULL ESTIMATED COST                                   148.55     710.47

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                     0.00     -36.45
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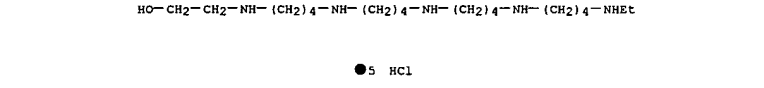
L16 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2003 ACS
AB Polyamine effectors are administered locally to provide protection against
the adverse side-effects of chemotherapy or radiation therapy, such as alopecia, mucositis and dermatitis. Pharmaceutical prepns. comprising one
or more polyamine effectors formulated for topical or local delivery to epithelial or mucosal cells are disclosed. Methods of administering the pharmaceutical prepns. are also disclosed.
ACCESSION NUMBER: 2003:132928 CAPLUS
DOCUMENT NUMBER: 138:180759
TITLE: Polyamines and analogs for protecting cells during cancer chemotherapy and radiotherapy
INVENTOR(S): Fahl, William E.; Kink, John A.
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013245	A1	20030220	WO 2002-US25216	20020807
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003118539	A1	20030626	US 2002-214917	20020807

PRIORITY APPLN. INFO.: US 2001-310634P P 20010807
US 2001-317768P P 20010906
US 2001-337382P P 20011105
US 2001-342932P P 20011220

IT **304911-06-6**, SL 11141
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamines and analogs for protecting cells during cancer chemotherapy
and radiotherapy)
RN 304911-06-6 CAPLUS
CN 3,8,13,18,23-Pentaazapentacosan-1-ol, pentahydrochloride (9CI) (CA INDEX NAME)



●5 HCl

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2003 ACS (Continued)

L16 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS
AB Polyamine or polyamine analog-amino acid conjugates (M)-N(E)-(B-A-B-NH)4-E
or (M)-N(E)-(B-A-B-NH)3-B-A-B-N(M)-E [M is an amino acid; A is a bond, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, or cycloaryl; B is a bond, alkyl, or alkenyl; E is H, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, or cycloaryl], including salts or stereoisomers, were prepd. for use as antiviral agents.
An example is the polyamine glutamine conjugate SL-11165 [NH2CH(CH2CH2CONH2)CON(Et)(CH2CH2CH2CH2NH)4Et.bul.5HCl]. Thus, (E)-EtNH(CH2)4NHCH2CH:CHCH2NH(CH2)4NHEt was prepd. by a multi-step sequence starting from 4-bromobutanenitrile, N-(mesitylsulfonyl)ethanamine, and (E)-2-butene-1,4-diol.
ACCESSION NUMBER: 2002:888472 CAPLUS
DOCUMENT NUMBER: 137:384565
TITLE: Preparation of polyamine or polyamine analog-amino acid conjugates as antiviral agents
INVENTOR(S): Frydman, Benjamin; Marton, Laurence J.; Valasinas, Aldonia L.; Reddy, Venodhar K.; Gutierrez, Jesus A.
PATENT ASSIGNEE(S): Slil Biomedical Corporation, USA; Eli Lilly & Company
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002091989	A2	20021121	WO 2001-US43887	20011108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2000-246804P P 20001108
OTHER SOURCE(S): MARPAT 137:384565
IT **304911-06-6P**, SL 11141
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polyamine or polyamine analog-amino acid conjugates as antiviral agents)
RN 304911-06-6 CAPLUS
CN 3,8,13,18,23-Pentaazapentacosan-1-ol, pentahydrochloride (9CI) (CA INDEX NAME)

●5 HCl

L16 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS
AB The polyamines spermidine and spermine and their diamine precursor putrescine are essential for mammalian cell growth and viability, and strategies are sought for reducing polyamine levels in order to inhibit cancer growth. Several structural analogs of the polyamines have been found to decrease natural polyamine levels and inhibit cell growth, probably by stimulating normal feedback mechanisms. In the present study,
a large selection of spermine analogs has been tested for their effectiveness in inducing the prodn. of antizyme, a key protein in feedback inhibition of putrescine synthesis and cellular polyamine uptake.
Bisethylnorspermine, bisethylhomospermine, 1,19-bis-(ethylamino)-5,10,15-triazanonadecane, longer oligoamine constructs and many conformationally constrained analogs of these compds. were found to stimulate antizyme synthesis to different levels in rat liver HTC cells, with some producing far more antizyme than the natural polyamine spermine. Uptake of the tested compds. was found to be dependent on, and limited by, the polyamine
transport system, for which all these have approx. equal affinity. These analogs differed in their ability to inhibit HTC cell growth during 3 days
of exposure, and this ability correlated with their antizyme-inducing potential. This is the first direct evidence that antizyme is induced by several polyamine analogs. Selection of analogs with this potential may be an effective strategy for maximizing polyamine deprivation and growth inhibition.
ACCESSION NUMBER: 2002:795681 CAPLUS
DOCUMENT NUMBER: 138:297219
TITLE: Antizyme induction by polyamine analogues as a factor of cell growth inhibition
AUTHOR(S): Mitchell, John L. A.; Leyser, Aviva; Holtorff, Michelle S.; Bates, Jill S.; Frydman, Benjamin; Valasinas, Aldonia L.; Reddy, Venodhar K.; Marton, Laurence J.
CORPORATE SOURCE: Department of Biological Sciences, Northern Illinois University, DeKalb, IL, 60115, USA
SOURCE: Biochemical Journal (2002), 366(2), 663-671
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **304911-06-6**, SL 11141
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SL 11141; prepn. of and antizyme induction by polyamine analogs as factors for cell growth inhibition)
RN 304911-06-6 CAPLUS
CN 3,8,13,18,23-Pentaazapentacosan-1-ol, pentahydrochloride (9CI) (CA INDEX NAME)

●5 HCl

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS

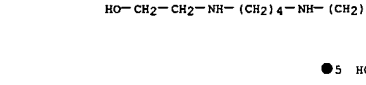
L16 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS
AB Conjugates of polyamines analogs conjugated to at least one amino acid of formula M-N(E)-(B-A-B-NH)4-E or M-N(E)-(B-A-B-NH)3-B-A-B-N(M)-E [wherein M
= independently an amino acid, esp. glutamine, asparagine, lysine, ornithine, arginine, histidine, or citrulline; A = independently a bond, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, or cycloaryl; B = independently a bond, alkyl, or alkenyl; E = independently H, (cyclo)alkyl, (cyclo)alkenyl, alkynyl, or cycloaryl; and salts or stereoisomers thereof]
were tested and claimed for pharmaceutical use as anticancer agents. For example, the polyamine glutamine conjugate SL-11165 [NH2CH(CH2CH2CONH2)CON(Et)(CH2CH2CH2CH2NH)4Et.bul.5HCl] exhibited ID50 values of >31.65, 4.1, and >31.25 against the DuPro, PC-3, and LnCap prostate cancer cell lines, resp. In addn., conformationally restricted polyamine analogs were prepd. Thus, (E)-EtNH(CH2)4NHCH2CH:CHCH2NH(CH2)4NH
Et was prepd. in a multi-step sequence starting from 4-bromobutanenitrile,
N-mesitylethanamine, and (E)-2-butene-1,4-diol.
ACCESSION NUMBER: 2002:368258 CAPLUS
DOCUMENT NUMBER: 136:386292
TITLE: Preparation of conformationally restricted polyamine analogs and use of polyamine amino acid conjugates as anticancer agents
INVENTOR(S): Frydman, Benjamin; Marton, Laurence J.; Valasinas, Aldonia L.; Reddy, Venodhar K.
PATENT ASSIGNEE(S): Slil Biomedical Corporation, USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002038105	A2	20020516	WO 2001-US43585	20011108
WO 2002038105	A3	20030227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002035126	A5	20020521	AU 2002-35126	20011108

PRIORITY APPLN. INFO.: US 2000-246804P P 20001108
WO 2001-US43585 W 20011108
OTHER SOURCE(S): MARPAT 136:386292
IT **304911-06-6P**, SL 11141
RL: SPN (Synthetic preparation); PREP (Preparation)
(polyamine; prepn. of conformationally restricted polyamines and use of
polyamine amino acid conjugates as anticancer agents)
RN 304911-06-6 CAPLUS
CN 3,8,13,18,23-Pentaazapentacosan-1-ol, pentahydrochloride (9CI) (CA INDEX NAME)

L16 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS (Continued)



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L16 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS
AB Microsporidia are eukaryotic obligate intracellular protists that are emerging pathogens in immunocompromised hosts, such as patients with AIDS or patients who have undergone organ transplantation. We have demonstrated in vitro and in vivo that synthetic polyamine analogs are effective antimicrosporidial agents with a broad therapeutic window. CD8-knockout mice or nude mice infected with the microsporidian Encephalitozoon cuniculi were cured when they were treated with four different novel polyamine analogs at doses ranging from 1.25 to 5 mg/kg of
body wt./day for a total of 10 days. Cured animals demonstrated no evidence of parasitemia by either PCR or histol. staining of tissues 30 days after untreated control animals died.
ACCESSION NUMBER: 2002:30291 CAPLUS
DOCUMENT NUMBER: 136:318859
TITLE: Novel synthetic polyamines are effective in the treatment of experimental microsporidiosis, an opportunistic AIDS-associated infection
AUTHOR(S): Bacchi, Cyrus J.; Weiss, Louis M.; Lane, Schenella; Frydman, Benjamin; Valasinas, Aldonia; Reddy, Venodhar; Sun, Jerry S.; Marton, Laurence J.; Khan, Imitiaz A.; Moretto, Magali; Yarlett, Nigel; Wittner, Murray
CORPORATE SOURCE: Haskins Laboratories and Departments of Biology and Chemistry, Pace University, New York, NY, 10038-1598, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2002), 46(1), 55-61
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **304911-06-6**, SL 11141
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SL 11141; novel synthetic polyamines are effective in treatment of exptl. microsporidiosis, opportunistic AIDS-assocd. infection)
RN 304911-06-6 CAPLUS
CN 3,8,13,18,23-Pentaazapentacosan-1-ol, pentahydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS

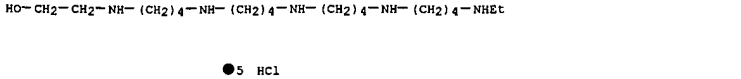
AB Novel conformationally restricted polyamines, such as E-NH-(B-A-B-NH)4-E [A, E = bond, alkyl, alkenyl, alkynyl, cycloalkyl, cycloaryl, cycloalkenyl; B = bond, alkyl, alkenyl], were prepd. for pharmaceutical use as anticancer agents. Thus, (E)-EtNH(CH2)4NHCH2CH:CHCH2NH(CH2)4NHEt was prepd. in a multistep sequence starting from mesityl chloride 4-bromobutanenitrile, N-mesitylethanamine, and (E)-2-butene-1,4-diol. The prepd. polyamines were tested for antiproliferative activity against human prostate cancer cell lines, such as PC3 and DUPRO.

ACCESSION NUMBER: 2000:790505 CAPLUS
DOCUMENT NUMBER: 133:350095
TITLE: Preparation of conformationally restricted polyamine analogs as disease therapies
INVENTOR(S): Frydman, Benjamin; Marton, Laurence J.; Reddy, Venodhar K.; Valasinas, Aldonia; Blokhin, Andrei V.; Basu, Hirak S.
PATENT ASSIGNEE(S): Slil Biomedical Corporation, USA
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066587	A2	20001109	WO 2000-US11591	20000427
WO 2000066587	A3	20010125		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1177197	A2	20020206	EP 2000-928583	20000427
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010701	A	20020213	BR 2000-10701	20000427
JP 2002543202	T2	20021217	JP 2000-615617	20000427

PRIORITY APPLN. INFO.: US 1999-131779P P 19990430
WO 2000-US11591 W 20000427
OTHER SOURCE(S): MARPAT 133:350095
IT **304911-06-6P**, SL 11141
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of conformationally restricted polyamines as antiproliferative prostate cancer agents)
RN 304911-06-6 CAPLUS
CN 3,8,13,18,23-Pentaazapentacosan-1-ol, pentahydrochloride (9CI) (CA INDEX NAME)

L16 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS (Continued)



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L16 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS

AB The invention relates to peptide conjugates in which cytocidal and cytostatic agents, such as polyamine analogs or naphthoquinones, are conjugated to a polypeptide recognized and cleaved by enzymes such as prostate-specific antigen (PSA) and cathepsin B. Methods of using these conjugates in the treatment of prostate diseases are also provided. Thus, C2[CH2NH(CH2)4NHEt]2.4HCl (SL-11103), 4-[[7-[4-(9-acridinylamino)phenyl]heptyl]oxy]-1,2-naphthoquinone (SL-11064), and morpholino-Ser-Lys-Leu-Gln-.beta.-Ala-.beta.-lapachone (SL-11147) were prepd. and assayed for antitumor activity against human prostate cancer cell lines, such as PC-3 and DUPRO.

ACCESSION NUMBER: 2000:790358 CAPLUS
DOCUMENT NUMBER: 133:350515
TITLE: Preparation of novel polyamine analog conjugates and quinone conjugates as therapies for cancers and prostate diseases
INVENTOR(S): Frydman, Benjamin; Marton, Laurence J.
PATENT ASSIGNEE(S): Slil Biomedical Corporation, USA
SOURCE: PCT Int. Appl., 194 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066175	A2	20001109	WO 2000-US11542	20000427
WO 2000066175	A3	20010802		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1173223	A2	20020123	EP 2000-928565	20000427
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010700	A	20020213	BR 2000-10700	20000427
JP 2002543163	T2	20021217	JP 2000-615058	20000427

PRIORITY APPLN. INFO.: US 1999-131809P P 19990430
WO 2000-US11542 W 20000427
OTHER SOURCE(S): MARPAT 133:350515
IT **304911-06-6P**, SL 11141
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of novel polyamine analog conjugates and quinone conjugates as therapies for cancers and prostate diseases)
RN 304911-06-6 CAPLUS
CN 3,8,13,18,23-Pentaazapentacosan-1-ol, pentahydrochloride (9CI) (CA INDEX NAME)

L16 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS (Continued)

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	32.59	743.06

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-4.56	-41.01

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